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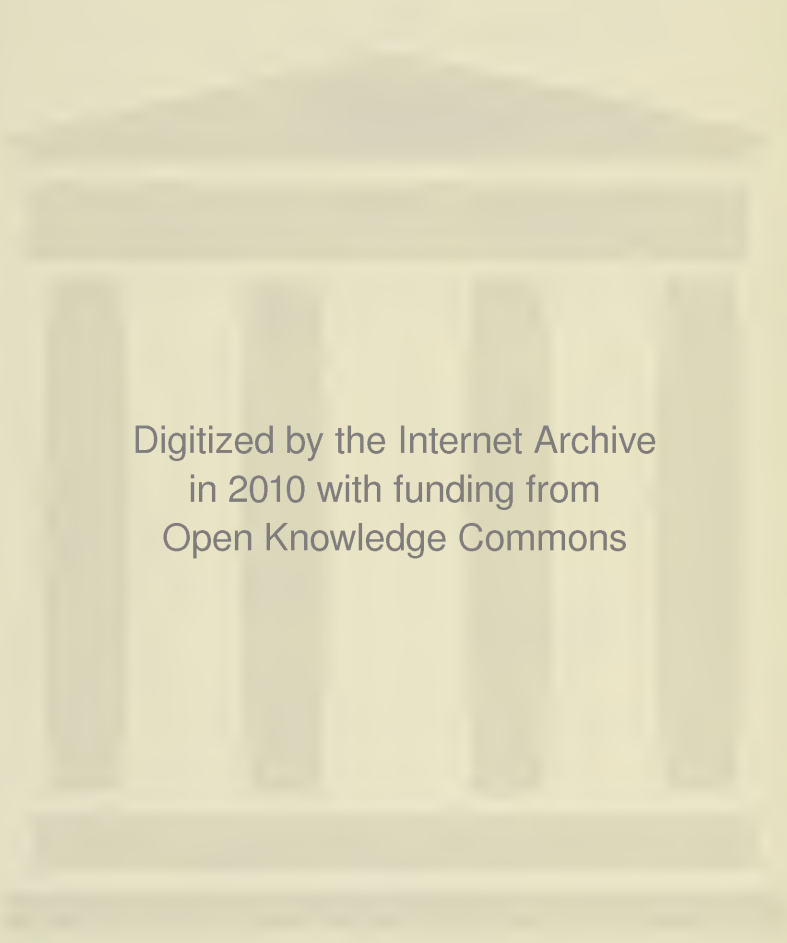

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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS

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VOLUME II

INFECTIOUS DISEASES

ILLUSTRATED

PHILADELPHIA AND NEW YORK

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INFECTIOUS DISEASES.

CHAPTER I.

INTRODUCTION TO THE STUDY OF INFECTIOUS DISEASES.

By LUDVIG HEKTOEN, M.D.

Certain minute organisms develop, which the eyes cannot see, and which (being disseminated) in the air enter into the body by way of the mouth and nostrils, and give rise to serious ailments.—VARRO, 116 to 27 B. C.

THE GENERAL NATURE AND SPECIFICNESS OF INFECTIOUS DISEASES.

By infection we generally understand the entrance into the body of living agents, capable of multiplication, most commonly microbes, which then cause disease.[1] It is true that sterile chemical substances of bacterial origin may produce the symptoms typical of certain infectious diseases, without infection being present in the usual sense. A good example is the production of tetanus by tetanus toxin without infection with tetanus bacilli. Spontaneous diseases of this kind are practically unknown, because the poisons do not occur in sufficient quantities free in nature. Human tetanus, it is true, has been caused by the injection of antidiphtheria serum drawn from horses in the period of incubation preceding the active symptoms of tetanus caused by natural infection. Experimentally the symptoms of diphtheria and tetanus are produced readily in susceptible animals by the injection of sterile toxins of the corresponding bacteria. Disease so produced is, however, not communicable in the sense that infectious diseases are, because the morbific agent —the toxin—is incapable of multiplication.

The conception of the specificness of the causes of infectious diseases probably arose early in the history of medicine. Leprosy, scabies, and hydrophobia were held to be transmissible diseases in early times. Later the observations on immunity and immunization helped to establish the individuality of smallpox, measles, and scarlet fever. The fact that survival of an attack of one disease protected against further attacks of that disease only, and against no other, as well as the results of inoculation in smallpox, pointed most clearly to the existence of specific causes, which were indicated by the specificness of the immunity. But only in modern times has the existence of a specific morbific agent been postulated for each infectious disease.

[1] In this article the strictly microparasitic infections alone are considered.

The earlier efforts to demonstrate the microbic causes of infectious diseases —1830 to 1870 about—met with great obstacles both from imperfect technical methods and the erroneous doctrine of spontaenous generation and the natural deduction based thereon; namely, that microbes present in the lesions of infectious processes were the products and not the cause of the diseases. When the doctrine of spontaneous generation was overthrown by Pasteur and others, there followed a period during which it was taught by some that the same bacterium was capable of existing in numerous forms endowed with different functional powers. The following citation from Nägeli illustrates clearly this idea of unlimited variability of microbes: "In the course of generation the same species assumes alternatingly different morphological and physiological forms which, as years and periods of years pass by, may cause now souring of milk, now the formation of butyric acid in sauerkraut, now the fermentation of wine, now the decomposition of albuminous matters, now the splitting up of urea, now the red color of starchy food, and give rise now to diphtheria, now to typhoid fever, now to recurrent fever, now to cholera, now to malarial fever." But the efforts to demonstrate the truth of this statement by experimental transformation of the harmless hay bacillus into the anthrax bacillus failed, and Nägeli's views soon lost support.

In the meantime Pasteur had demonstrated that certain forms of fermentation and decomposition are associated with definite organisms; and the introduction by Koch of solid media for the pure culture of bacteria was another long step forward in the establishment of the specificness of infectious agents. A means was now given for the careful study of the properties of bacteria, and the specific cause of many infectious diseases was studied and in several instances the etiological role established completely in accord with Koch's well-known laws. Very soon further evidence of the specificity of infectious microbes was secured, as the mechanisms of their pathogenic action, their chemistry, and the specific nature of the reactive products—antitoxins, lysins, agglutinins, precipitins—in the infected organism were subjected to careful study.

Modern studies of immunity have established the distinct and permanent individuality of infectious microbes, even in the case of those that cause inflammations now in one organ, now in another; and we have every reason to believe that an infectious disease that differs clinically and epidemiologically from other infectious diseases has its own peculiar specific cause.

INFECTIOUS AGENTS.

By pathogenic microörganisms we understand a number of different low forms of life that possess the important feature in common of causing infections in human beings and animals. The pathogenic microörganisms belong to various classes: some, like fungi, are low forms of vegetable life; the protozoa are unicellular forms of animal life; while the bacteria occupy a position midway between these two groups, resembling the fungi in their mode of nutrition, and flagellate protozoa in that some possess a locomotive apparatus consisting of flagella. In addition it has been shown recently that certain infectious diseases are caused by agents that, whatever their nature, pass through filters that hold back bacteria (filterable or ultramicroscopic virus).

Pathogenic Bacteria.—Of the various forms of pathogenic microörganisms the bacteria are the most important so far as concerns the infectious diseases whose etiology is understood clearly at the present time. In comparison with the endless number of saprophytic varieties, the number of pathogenic bacteria is so small that they are in reality quite exceptional. Of the numerous vibrios, for instance, practically only one, namely, the cholera vibrio, is pathogenic for man. There are all degrees of transition between the purely saprophytic bacteria and the pathogenic. Many saprophytes when introduced into the body in large number exercise a purely toxic effect without being infectious in the strict sense—that is, able to invade the tissues and there multiply.

From their parasitic relations, pathogenic organisms fall into three groups, namely: 1. Obligate parasites, which develop only within a living host (the bacillus of leprosy, the spirillum of relapsing fever, and the protozoa of malaria). 2. Facultative saprophytes—microbes that are ordinarily parasitic but able to grow outside the body under special conditions. The majority belong to this group, but there is no sharp distinction between obligate parasites and facultative saprophytes. The tubercle bacillus, for instance, may be cultivated artificially; but it is doubtful if it could grow outside the body under natural conditions. In these two groups the adaptations to parasitic life are highly perfected, and in many, perpetuation is dependent upon continuous transmission from host to host. 3. Facultative parasites—saprophytic organisms capable of some degree of parasitic existence, but so far as perpetuation of the species is concerned it appears to be a matter of little importance whether they invade the living body or not (B. tetani, B. aërogenes capsulatus, Amœba dysenteriæ). These various forms are regarded as the result of a phylogenetic parasitic adaptation. It is regarded as quite probable that all bacteria capable of so adapting themselves have done so already, and that no new disease will arise from new adaptations. The as yet poorly understood or wholly unknown causative agents of hydrophobia, variola, measles and scarlet fever, appear to be obligate parasites, and in the case of measles and scarlet fever the specific agents appear to find suitable conditions for propagation in man only.

Pathogenic Protozoa.—Important infectious diseases in man and animals are caused by protozoa; *e.g.*, malaria, amœbic dysentery, trypanosomiasis, piroplasmosis, and possibly yellow and scarlet fever. The study of pathogenic protozoa and their products has been confined so far within somewhat narrow limits because of our inability to grow these microörganisms in pure cultures on artificial media. However, decided progress has been made in overcoming this obstacle. In 1901, Lignieres observed that a considerable proliferation of Piroplasma bigeminum may be obtained by placing defibrinated blood, rich in the organisms, either at room temperature or in the incubator for ten to thirty days. He succeeded in obtaining subcultures to the fifth generation by inoculating "hæmoglobinæmic serum." So far this observation seems to have attracted little notice. In 1903, Novy and McNeal demonstrated that rat trypanosomes can be grown artificially on agar mixed with defibrinated rabbit's blood, and, soon after, that Trypanosoma Brucei could be cultivated in vitro in the same way.

Ultramicroscopic or Filtrate Virus.—Various reasons are assigned for the failure to discover the causes of many diseases of undoubted infectious nature. It has been suggested that some may be caused by a mixed or

symbiotic infection, the non-toxic products of two microbes uniting to form a specific toxic substance. At all events these infectious agents appear to be unstainable and uncultivatable by our present methods. The recent demonstration by Schaudinn of Spirochæte pallida in the lesions of syphilis again emphasizes the great value of special staining methods. There is good reason to believe that the chief reason for the invisibility of the agents concerned in many diseases of unknown etiology is due to their ultramicroscopic size. If the influenza bacillus were four to five times smaller, it could not be seen with the ordinary microscope. The organism of peripneumonia is so minute that it is barely visible; it occupies the border line between the visible and the invisible.

It has been shown that the viruses of foot-and-mouth disease, peripneumonia, rinderpest, sheep-pox, chicken-typhus, horse-sickness, epithelioma contagiosum in fowls, yellow fever, hydrophobia, and hog cholera,[1] pass through various filters ordinarily regarded as impermeable to the smallest known bacteria. The filtrates give no morphological sign of containing visible corpuscular elements (except in peripneumonic virus), are virulent, and the diseases so caused are transmissible and hence truly infectious. The only virus of this group that has been cultivated is that of peripneumonia.

The viruses of smallpox and vaccinia and of the so-called Rocky Mountain fever are not filterable. Scarlet fever, measles, chickenpox and typhus fever are not transferable to animals, so that the question of filterability of their viruses remains open.

Infectious Chemical Agents.—Benjamin Moore believes that certain infectious diseases of unknown etiology may be caused by enzymes. He finds in autocatalysis an example of a chemical action that explains the apparent reproduction of the virus in infectious diseases. In autocatalysis the reaction at first proceeds very slowly, gradually acquiring increasing speed as the products accumulate. When copper or mercury come in contact with nitrous acid there is at first no evident action, but as nitrous acid develops, it acts catalytically, increasing the velocity of reaction and its own production at the same time Now, says Moore, there may be abnormal cellular reactions of similar catalytic character that produce the same bodies as those necessary to promote the reaction. As this "chemical virus" increases in amount it may cause the clinical picture of the disease, and on passage to other susceptible persons the same process would repeat itself. As yet this interesting theory is without experimental proof.

THE SOURCES OF INFECTIOUS AGENTS, AND THE WAYS AND MEANS OF INFECTION.

At the present time the common all-important source of the microbes that cause infectious diseases is the sick man or animal from which the

[1] De Schweinetz and Dorset (Bureau of Animal Industry, 1903, Circular 41) showed that the real cause of hog cholera passes through "the finest porcelain filters." This remarkable observation is confirmed by Boxmeyer (*Journal of Infectious Diseases*, 1905; vol. ii, p. 359), and by Dorset, Bolton, and McBryde (Bureau of Animal Industry, 1905, *Bulletin* 72). The latter observers are inclined to regard the hog-cholera bacillus, hitherto accepted as the essential cause of hog cholera, as a secondary invader.

microbe may pass to other individuals and start new infections either by direct or indirect transfer. Prevention of infectious diseases rests on a knowledge of the mode of spreading and the more accurate and complete this knowledge, the more effective becomes our prevention. Only a few pathogenic germs lead a regular saprophytic existence. The bacilli of tetanus, of botulism and of emphysematous gangrene, may inhabit the intestinal contents of the larger animals and man, and occur in many soils, especially where manure is deposited. The action of B. tetani is essentially toxic, and it has hardly any invasive powers. The gas bacillus and other anaërobic bacteria with pathogenic powers, are also essentially saprophytic in their habits, and perpetuate themselves without difficulty outside the body.

Occurrence of Pathogenic Bacteria on Healthy Human Beings and in the Internal Organs of Healthy Animals.—So long as microbes remain wholly upon the surface of the body, either externally or internally, they are not able to produce disease. The skin and the mucous membranes which communicate with the external air constantly harbor bacteria capable of causing disease under suitable conditions. The principal pathogenic bacteria present on the skin and mucous membranes of man are streptococci, staphylococci, pneumococci, diphtheria bacilli, colon and influenza bacilli, and certain pathogenic anaërobes. Streptococci and pneumococci of undoubted pathogenic possibilities are present upon the tonsils. Certain staphylococci always occur on the skin. Pneumococci occur in the saliva of a considerable percentage of healthy persons, and also on the tonsils in conjunction with streptococci and perhaps with equal frequency. Diphtheria bacilli may be found in the throats of normal persons, especially in connection with outbreaks of the disease in schools and other institutions. Tubercle bacilli have been found upon the nasal lining and skin of healthy persons. Meningococci have been found in the nasal mucus in a considerable percentage of persons in close contact with patients suffering from epidemic cerebrospinal meningitis. In outbreaks of typhoid fever, Asiatic cholera, and dysentery, when the bacilli of these diseases are disseminated freely, it is not unusual to find them in the intestinal contents of individuals who do not suffer from infection. Persons who have recovered from typhoid fever may harbor typhoid bacilli in the urine and the bile for months and even years. These facts illustrate the manner in which healthy persons may convey specific infectious germs to those that are susceptible.

It is stated generally that the internal organs of healthy animals are free from bacteria, and this is the conclusion reached by Neisser, Opitz, and others. Others, however, have reached different conclusions. Kälbe found that in hogs the peribronchial lymph glands commonly contain pneumococci, capsulated bacilli, and pyogenic organisms. Tubercle bacilli have been found in normal human lymph nodes by Harbitz. Ford found that the internal organs of rabbits, guinea-pigs, dogs, and cats, yielded cultures in over half of the cases, and his experiments were made under conditions that appear to have excluded the possibility of contaminations. In most instances it concerned intestinal forms; staphylococcus aureus was found, and in cats and dogs certain peculiar unidentified bacteria were present. Fasting animals give more sterile organs than those that were eating. Whether all these bacteria are to be regarded as continuous invaders from mucous surfaces, or whether some of them at least constantly inhabit the tissues, are undecided questions, as are also their relations to actual infections. Wrzosek,

who cultivated bacteria from various internal organs of a considerable proportion of the animals investigated, most numerously in dogs, believes that the bacteria come principally from the intestinal tract and that this form of "physiological infection" explains many puzzling cases of cryptogenetic infection.

Transmission of Infection by Animals.—Animals may cause human diseases in three different ways. In the first place, they may suffer from diseases directly or indirectly transferable to man; *e. g.*, anthrax, tuberculosis, glanders, pest. In the second place, animals, especially flies, may act as mechanical carriers of germs in such a way that contact or food infection of human beings occur. Suctorial insects may transfer infective material from the sick to the well. In the third place, certain animals, especially mosquitoes, act as intermediary hosts for pathogenic protozoa and organisms of as yet unknown nature, which here pass through developmental cycles and acquire infectious powers so that they cause disease when deposited again in the tissues of susceptible persons, as in malaria and yellow fever. The first demonstration of an intermediate host of this kind was made by Theobald Smith and Kilbourne, who showed that the parasite of Texas fever in cattle is transmitted by a tick. Their work paved the way for the demonstration of the role that the mosquito for some time has been suspected of playing in malaria and also in yellow fever. Trypansomiasis and peroplasmosis have also been shown to be conveyed by certain flies and ticks, but in trypanosomiasis at least the insects appear to play but a passive part.

Aërial Infection.—Infectious microörganisms may be deposited on the ground or floor, on clothing, and on articles of various kinds. There is abundant evidence that the acute exanthematous diseases, wound infections, pest, diphtheria, typhoid fever, and other diseases, may be carried by infected clothing and other articles. In most of these cases it concerns the conservation of microbes in virulent form rather than actual multiplication; cholera and typhoid bacilli may multiply perhaps in fæcal masses deposited on clothing. Until a few years ago aërial infection was regarded universally as infection by dust, carrying dried bacteria. Cornet called our notice to the dangers of dried tuberculous sputum. In 1897 Flügge began a series of investigations of the air as the carrier of infection, the results of which established that air may convey bacteria not only when dry, as dust, but also in fine bubbles or droplets of sputum or moisture. Of these two forms the second is probably the more important in spreading disease in general.

Dust Infection.—True dust infection requires that the organism withstand drying in the air to the extent that it can be whirled about and carried for some distance by air currents. Dry bacteria of this kind constitute the real danger in dust infection as now understood. Of course strong currents, mechanical disturbances of accumulated matter, "dry dusting," violent shaking and rubbing of handkerchiefs and other contaminated articles, may set in motion for a time larger particles containing infectious materials, but these would rapidly settle down, when it is true, they might cause infection from direct contact; whereas it has been shown that smaller particles of completely dried material may remain suspended for three or four hours, and herein lies one of the chief elements of danger of this mode of infection.

Largely upon the basis of the results obtained by Neisser, Gotschlich divides pathogenic bacteria with reference to their power to communicate disease when dry as follows:

1. Bacteria that are not viable in air-dried dust and which consequently cannot disseminate disease in dust:—cholera vibrio, gonococcus, pest and influenza bacilli.

2. Bacteria that withstand drying and may convey disease when carried by such air currents as occur in ordinary houses (1 to 4 mm. per second): meningococcus, pyogenic cocci, bacillus pyocyaneus, tubercle bacillus, tetanus bacillus, and anthrax spores.

3. Bacteria that withstand drying but are disseminated only by so strong currents as rarely occur in houses: diphtheria bacillus, typhoid bacillus.

It must be added that cutaneous debris and other material conveying measles, scarlet fever, and smallpox, are disseminated readily in dust. English observers lay great stress on the "aërial convection" of smallpox. In measles and scarlet fever the danger of aërial infection is confined to within a few feet from the patient.

Droplet Infection.—Flügge and his coworkers have demonstrated that in talking, coughing, and sneezing, numerous germ-laden bubbles of mucus and saliva pass out into the air, where they may float about for a time. The distance to which these may pass depends on the force with which they are expelled, the nature of the air currents, and the size and weight of the droplets. Koeniger found that after rinsing the mouth with a suspension of B. prodigiosus, droplets containing bacilli were carried as far as 12.4 meters. Tuberculous patients rarely throw out droplets farther than 1.5 meter, and this is the limit within which association with coughing consumptives must be regarded as positively dangerous. As regards droplet infection relatively strong patients who walk about may be just as dangerous as the weak and bedridden and even more so. On account of the viscid character of tuberculous sputum the droplets on drying adhere firmly, and it seems that mechanical influences are necessary in order to loosen particles from dry drops. Tubercle bacilli may remain alive for eighteen days in drops that dry in the dark, and for three days in the light.

Numerous pathogenic germs may be disseminated by droplets or bubbles of mucus and saliva, among them most of those that die on drying. It is likely that influenza, pneumonia, diphtheria, whooping-cough, measles, scarlet fever, and smallpox, are communicated freely in this way, and probably also epidemic meningitis. Streptococci may be expelled to various distances in talking, coughing, and even in rapid breathing, and undoubtedly operative infections may be caused in this way. It is also probable that in hospital wards especially, virulent streptococci and pneumococci may be communicated through droplet infection. Schaeffer found that patients with leprous lesions in the mouth and respiratory tract may expel large numbers of lepra bacilli in droplets of mucus. Aërial infection of whatever character is most dangerous by far in closed rooms, railway cars and shops. In the open it is far less likely to occur because of the unlimited space, the strong currents of air, and the action of sunshine.

Water-borne Infection.—Water plays an essential role in the dissemination of typhoid fever, cholera, bacillary and amœbic dysentery. It is only exceptionally that actual bacterial multiplication takes place. In India the temperature and amount of vegetable and other materials in the waters of the Ganges enable the cholera spirilla to multiply. In most waters in temperate climates the bacteria are able to maintain life only for a comparatively short time. It is said, largely as the result of laboratory experiments,

that cholera germs will remain alive in water under "natural conditions" for three months, and typhoid bacilli for four weeks. In the experiments of Jordan, Russell, and Zeit, in which typhoid bacilli were exposed to canal and river waters in sacs permeable to dissolved substances, the bacilli perished as a rule within three to four days. Theoretically it may be possible that resistant bacteria may withstand for a longer period the specially hostile influences in water.

The Soil and Infection.—According to Pettenkoffer's theory the subsoil played an essential part in the dissemination of infectious diseases; but this theory has been abandoned because it has been shown conclusively that pathogenic germs do not reach and cannot live in the deeper layers of the soil, which normally are sterile. Experimentally it has been found that typhoid and cholera bacteria may retain their viability for some time when deposited in the superficial layers of the soil. Rullmann found that typhoid bacilli implanted in sterile sand remained alive at the end of eighteen months when the material had dried completely. Levy and Keyser have shown that the contents of privy vaults containing typhoid bacilli may be dangerous even after months. Anthrax bacilli may live for a long time in the ground, where they pass into spore forms which may infect susceptible animals. The superficial layers of manured soil also harbor pathogenic anaërobic organisms, of which the most important are the tetanus and the gas bacillus.

Food and Infection.—Various pathogenic bacteria may occur in foods. These may be derived from animals, as tubercle, anthrax, glanders and paratyphoid bacilli and streptococci. Food, especially milk, originally quite pure, is frequently contaminated on its way to the consumer. Diphtheria bacilli and the cause of scarlet fever may be disseminated as the result of direct contamination of milk, or it may be more indirect, as by the use of infected water in cleansing utensils, etc., and in this way typhoid, cholera, and dysentery bacteria may be conveyed. Milk is a peculiarly dangerous medium because it furnishes conditions favorable for microbic multiplication. Oysters and other shellfish may convey typhoid bacilli from polluted waters. In recent cholera epidemics, especially in the Philippine Islands, the disease was spread through food to a larger extent than by contaminated water. Non-infective but toxicogenic saprophytes may multiply in milk, dairy products, meat, and fish, which, when consumed, thus may cause severe—often fatal—forms of acute intoxication. Recently paratyphoid bacilli have been found to play an important role in meat poisoning, and in some of these cases the symptoms are typhoid-like; other cases are more acute. Here it appears to concern the meat of cattle infected during life. From Malta it is reported that Malta fever probably is communicated by the milk of goats that have the disease.

ROUTES OF INFECTION.

Pathogenic microörganisms may enter the body by its external and internal surfaces. The intact skin offers mechanical protection against all microbes, and so far as we know there are probably none that can invade the body through the healthy skin without causing at the same time some lesion at the point of entrance. Bacteria may find conditions favorable for lodgment in the gland ducts and hair follicles of the skin. It has been shown

experimentally that when Staphylococcus pyogenes aureus and other bacteria are rubbed energetically into the skin, they may enter openings of gland ducts and cause furuncles. In nursing women staphylococci frequently enter the milk ducts. Pest bacilli cause fatal infections when applied to the shaven but otherwise undamaged skin of guinea-pigs but the possibility of minute wounds cannot be excluded.

Minute wounds often form points of entrance for infection as is thought to occur as a rule in bubonic pest; but the actual wounds are rarely demonstrable, the bubo being the primary localization. The pulling out of hair on the lips is sometimes followed by exceedingly virulent forms of staphylococcus infections, the so-called carbuncles of the lips. Actively bleeding wounds are relatively less dangerous, because the germs that may be present are washed away by the blood. Experimentally it has been demonstrated that when bacteria (anthrax bacilli) enter the bloodvessels of the skin general dissemination occurs within a few moments. The removal of tension by open treatment and drainage greatly lessens the danger of infection through wounds. Crushing wounds are always dangerous, and clotted blood in the depths favors the development of tetanus; contused and crushing wounds in general are favorable to anaërobic infection. Healthy intact granulation tissue offers complete protection to ordinary infections according to the experiments of Afanassieff and others. In the new-born the germs of general infection frequently enter by way of the navel. In addition to ordinary wound and septic infections the skin is the place of entrance for those diseases communicated regularly by the bites of insects.

In spite of the protection offered by the flow and the slight bactericidal action of tears, the conjunctiva is frequently the seat of local infections with various organisms, including the pyogenic cocci, the gonococcus, etc. The experiments of Römer indicate that general infection probably does not occur directly from the conjunctiva but indirectly by the nasal mucous membrane, to which the organisms are carried by tears through the tear ducts. Small epithelial lesions caused by dust are regarded as favorable to local conjunctival infections, but gonococci are capable of infecting the intact conjunctiva of new-born children. General infections probably do not occur through the cornea. The loose structure, the great extent of the numerous recesses and folds, and the lymphatic tissues of the nasopharyngeal mucous membrane, render it, in spite of the protective action of the nasal mucus, an important entrance point for infectious organisms, some of which, *e.g.* tubercle bacilli, are able to pass through without previous injury. From the nasal mucosa microörganisms may pass into the meninges through the cribriform plate, and in this way it has been thought epidemic and other forms of meningitis may originate. It also seems possible that meningococci may find their way to the cerebrospinal membranes by way of the blood. Infections may extend also to the middle ear through the Eustachian tube.

The nasal lining may receive infection from the conjunctiva, and the German pest commission found that in rats general infection with pest bacilli occurs with the greatest readiness from the intact conjunctiva and from the nose. Leprosy and glanders commonly develop primarily in the nasal mucosa. The elimination of lepra bacilli in enormous numbers, in nasal mucus, points to this as a most important source for means of dissemination of this disease. The virus of measles localizes in the nose.

TABULAR SUMMARY OF THE WAYS AND MEANS OF INFECTION IN THE MOST IMPORTANT HUMAN INFECTIOUS DISEASES.

(Modified after Gotschlich.)

disease.	Direct contact with sick.	Latent cases.	Indirect contact.	Drinking-water.	Food.	Air infection.		Soil.	Animals.		
						Dust.	Droplet.		Intermediate hosts.	Infected animals.	As carriers.
Angina.	Common mode.	Yes.	Yes.	———	Yes.	Yes.	Common mode.	———	———	———	———
Anthrax.	Yes.	———	Yes.	———	Yes.	Yes.	Yes.	Yes.	———	Cattle, sheep.	Flies.
Cholera.	Yes.	Yes.	Yes—wash-linen, bedding, utensils, etc.	Common mode.	Yes.	———	———	———	———	———	Flies.
Diphtheria.	Common mode.	Yes—convalescents sometimes dangerous for a long time.	Yes—bedding, wash, playthings.	———	Yes.	Yes.	Common mode.	———	———	———	Flies.
Dysentery (bacillary and amœbic).	Yes.	Yes.	Yes—especially bacillary—wash-linen, bedding, utensils, etc.	Yes—especially amœbic.	Yes.	———	———	———	———	———	Flies.
Erysipelas.	Yes.	Yes.	Yes	———	Yes.	———	Yes.	———	———	———	———
Glanders.	Yes.	———	Yes.	———	———	———	Yes.	———	———	Horses.	———
Gonorrhœa.	Essential mode.	Yes.	Yes.	———	———	———	———	———	———	———	———
Influenza.	Essential mode.	Convalescents dangerous for long time.	Yes.	———	———	?	Typical mode.	———		———	———
Leprosy.	Common mode.	———	Yes?	———	———	?	Yes?	———	———	———	?
Malaria.	———	Latent cases important as source for dissemination by mosquitoes.	———	———	———	———	———	———	Only mode—mosquitoes.	———	———
Malta fever.	———	———	———	———	Yes, goat milk.	———	———	———	———	Goats.	———
Measles.	Common mode.	Yes.	Yes.	———	———	Yes.	Yes.	———	———	———	———
Meningitis (epidemic).	Common mode.	Yes.	Yes.	———	———	?	Yes.	———	———	———	Flies possibly.
Mumps.	Yes.	Yes.	Yes.	———	———	———	Yes.	———	———	———	———
Paratyphoid.	Yes.	Yes.	Yes.	Yes.	Yes, meat, milk.				———	Cattle.	

Tabular Summary of the Ways and Means of Infection in the Most Important Human Infectious Diseases.—Continued.

Pest.	Yes (pest pneumonic).	———	Yes,—infected clothing, rags, washlinen, rooms.	———	——	——	In pest pneumonia.	——	——	Rats, mice.	Flies fleas.
Pneumonia.	Common mode.	Yes.	Yes.	———	——	Yes—scales.	Yes.	——	——		——
Rabies.	Only mode.	———	———	———	——	——	———	——	——	Dogs, etc.	——
Relapsing Fever.	Common mode.	Yes.	Yes.	———	——	——	———	——	——	——	Bed-bugs. fleas,
Rocky Mountain Fever ("Spotted Fever").	———	———	———	———	——	——	———	——	Ticks.	——	Ticks.
Scarlet Fever.	Common mode.	Yes.	Yes.	———	Yes, milk.	Yes—scales.	Yes.	——	——	——	——
Syphilis.	Only mode.	Yes.	Yes.	———	——	——	———	——	——	——	——
Tetanus.	———	———	———	———	——	——	———	Yes.	——	——	——
Trachoma.	Common mode.	Yes.	Yes—handkerchiefs, towels, etc.	———	——	Yes.	———	——	——	——	Flies.
Trypanosomiasis.	———	———	———	———	——	——	———	——	——	——	Tsetse-fly.
Tuberculosis.	Yes.	Yes.	Yes—carpets, handkerchiefs, etc.	———	Yes—milk?	Yes.	Common mode.	——	Cattle?	——	Flies.
Typhoid Fever.	Rarely.	Important; especially urine after recovery.	Important.	Common mode.	Yes.	Yes.	Yes—typhoidal pneumonia.	Yes.	——	——	Flies.
Typhus.	Common mode.	Yes.	Yes—rags, linen, etc.	———	——	?	Yes.	——	——	——	Biting insects?
Variola.	Common mode.	Yes.	Yes.	———	——	Yes.	Yes.	——	——	——	——
Whooping-Cough.	Essential mode.	Convalescents dangerous for long time.	Yes.	———	——	?	Typical mode.	——	——	——	——
Wound Infection.	Yes.	Yes.	Yes.	———	Yes.	Yes.	Important—danger from healthy persons.	Yes.		——	——
Yellow Fever.	———	Latent cases important as source for dissemination by mosquitoes.	———	———	——	——	———	——	Only mode—mosquitoes.	——	——

The lining of the mouth is resistant to infection, and this is further hindered by the bactericidal and mechanical action of the saliva and mucus. In the new-born, in whom the epithelium is delicate, a mild form of gonococcal infection of the mouth may establish itself. When vital resistance seems to be greatly reduced, conditions arise in the mouth and throat that are favorable for the development of ulceromembranous and necrotic (noma) processes in which anaërobic bacteria take part. The oral mucous membrane is the most common seat of primary actinomycosis, which probably develops from the implantation of the organisms with bits of straw in the gums. Kolle found that in rats, pest bacilli enter readily by way of the oral mucous membrane and give rise to submaxillary buboes. The tonsils are important points of entrance of many infections, due, at least in part, to their exposed position, their deeply corrugated surfaces, and the imperfect epithelial lining. Streptococci and pneumococci occur upon the surface normally. The tonsils are the usual seat of invasion of scarlet fever and diphtheria, which are associated with a more or less well marked streptococcal angina. Acute rheumatism, infectious osteomyelitis, and obscure general infections, are often traceable to the tonsils because of initial angina. Undoubtedly the tonsils are the most important source of the general terminal streptococcus invasion that occurs so commonly, especially in smallpox and scarlet fever. While primary tonsillar tuberculosis appears to be rare, the recent researches of Harbitz show that the tonsils and other pharyngeal lymph nodes are important points of entrance for tubercle bacilli in early life.

Flügge and his coworkers have shown that bacteria—B. prodigiosus, tubercle bacilli—when inhaled either in the form of an artificial spray or dry dust, or contained in minute droplets, may be carried into the bronchi and pulmonary alveoli. Forced inspiration may suffice to carry pathogenic germs from the mouth into the finer bronchi. Undoubtedly droplet or inhalation infection plays a most important role in the various pneumonias (pneumococcal, pest, influenza). In some cases it is difficult to distinguish between pulmonary infections from without and those that come by way of the blood or lymphatic system. Paralysis of the cilia of the bronchial epithelium from various causes, among them cold, has been suggested as a predisposing cause of bronchopulmonary infection. The inhalation of dust particles is thought to aid the development of infection by causing minute injuries to the epithelium.

The gastric mucous membrane is resistant to infection principally on account of the gastric juice, which, when normal, may destroy bacteria or at least hinder their development in the stomach Koch and others found that feeding sheep with spore-free anthrax bacilli gave negative results, whereas feeding with spores resulted in anthrax. The cholera vibrio is especially susceptible to the acid gastric juice, the typhoid bacillus less so; but when the stomach is empty, or the seat of digestive disturbances, both these organisms may pass through unharmed. The gastric as well as the pancreatic juices destroy diphtheria and tetanus toxin, but have little or no effect upon the botulismus toxin.

Numerous important infectious diseases have their point of entrance in the intestines. cholera, typhoid, dysentery, and, in animals, anthrax, chicken cholera, and various hemorrhagic septicæmias. In cholera and bacillary dysentery the intestinal mucous membrane is the only point of

localization, and it is probable that typhoid bacilli commonly enter the body by way of the lymph nodes in the intestinal mucosa. This selective invasiveness is difficult to explain. In some persons there appears to be a local immunity to cholera, dysentery, and typhoid bacteria, for in time of epidemics certain individuals may harbor these organisms in their intestines without any evidence of invasion. While cholera vibrios and dysentery bacilli have special affinity for the intestinal mucosa, the bacilli of tetanus and of emphysematous gangrene, which often occur in the intestines, do not have the power to penetrate the normal intestinal epithelium. Under pathological conditions and after death the gas bacillus may pass into the tissues and the blood, and most cases of "foamy organs" are attributed to agonal or postmortem invasion of the gas bacillus from the intestines. Somewhat similar conditions appear to obtain with reference to the colon bacillus, which, however, probably has a greater invasive power. Tubercle bacilli are absorbed from the gastro-intestinal tract, and the primary localization may occur in the neighboring or remote lymph nodes and possibly the lungs without necessarily leaving any lesions at the point of entrance. When tubercle bacilli are fed to animals they appear to pass quickly through the intact mucous membrane into the chyle vessels and thoracic duct (Ravenel, Nicolas and Descos). The investigations concerning the absorption of bacteria from the gastro-intestinal canal in animals have given somewhat contradictory results, and there seems to be no reason to assign to this tract any greater role as a gateway for general infections than to other mucous membrane and the skin.

The genitals are the special seat of gonorrhœal and syphilitic invasion, but further than this play no peculiar role in the development of definite infectious diseases. The gonococcus is able to penetrate into the intact mucous lining of the urethra. The vagina is well protected against infection not only by its squamous epithelium, but also by the strongly bactericidal action of its acid secretion (Döderlein, Krönig and Menge). After parturition the female genital canal offers favorable chances for septic infection on account of the tears in the mucosa and the denudation of the uterus.

Many pathogenic organisms are able to cause infection only when introduced in a certain way or localized upon particular parts. Thus the cholera vibrio and the bacillus of dysentery are able to localize upon the intestinal epithelium only. The gonococcus invades those parts only of the genital tract that are clothed with cylindrical epithelium. The influenza bacillus lives almost exclusively upon the respiratory tract. Predilections for particular portals of entry are shown also by the organisms of diphtheria, pneumonia, tuberculosis, typhoid fever, etc., although many of them are capable of invasion along various channels. The reasons for these interesting adaptations must be sought in the biochemistry of the microörganisms and tissues in question.

It is interesting to note that those parts to which an organism is more or less specifically adapted may contain the same microbe or closely related forms in an attenuated or harmless state. Examples are the occurrence of so-called non-virulent diphtheria bacilli and of pseudodiphtheria bacilli in normal throats; of pneumococci and streptococci in the throat; of influenza-like bacilli in the respiratory tract; of gonococcoid cocci in the urethra; and of the various paratyphoid, paradysentery, and cholera-like bacteria in the intestines.

The bacillus of leprosy has a particular affinity for nerves, and the organism or poison of acute articular rheumatism for synovial membranes. Tetanus and hydrophobia develop from wound infections only, and the symptoms of these diseases become apparent when the tetanotoxin and the agent of hydrophobia have penetrated into the central nervous system. We know that there is a strong chemical affinity between the tetanotoxin and the neurocytes.

By *germinal infection* is meant an infection of the embryo by an infectious agent conveyed either by the ovum or the semen. It has been accepted that syphilis is transmissible to the fœtus by the sperm as well as by the ovum but some authorities claim that the mother is always the direct source of congenital syphilis. There is no satisfactory evidence that tubercle bacilli may be transmitted by germinal infection. Pathogenic microbes may pass from mother to fœtus and probably practically always by way of the placenta. Intra-uterine or placental infection of the fœtus has been observed to take place in smallpox, measles, scarlet fever, syphilis, typhoid fever, relapsing fever, pneumonia, anthrax, pyogenic infections, dysentery, and tuberculosis. In animals the organisms of chicken-cholera, glanders, symptomatic anthrax, anthrax, tuberculosis (relatively frequent in calves), etc., are transmissible by way of the placenta, but on the whole this form of infection is quite exceptional. Various preëxisting lesions in the placenta may favor placental transmission of microörganisms capable of causing injury to the placenta and of growing through unruptured vascular walls. The conditions of the circulation in the placental and uterine sinuses favor the collection there of bacteria that may be circulating in the maternal blood.

The claim by Baumgarten that tuberculosis in the offspring of tuberculous mothers is the result of an intra-uterine invasion, the bacilli remaining latent in the organs and tissues of the child, has not received any general support. The number of authentic cases of congenital tuberculosis is still small, although the list is growing. Harbitz has shown that there may be latent animal-virulent tubercle bacilli in normal human organs, but the determination of the possible duration of such latency presents great difficulty on account of the ever-present opportunities for postnatal invasion.

THE DISSEMINATION OF PATHOGENIC GERMS IN THE INFECTED BODY.

In their distribution in the body the various microörganisms follow different types, some being quite rigid in this respect, others able to follow more than one type. The most perfect example of strictly local distribution is furnished by the tetanus bacillus, which, when introduced into the tissues, causes only slight local changes and exhibits no, or very insignificant, invasive powers, the symptoms being all due to the absorption of tetanotoxin. In many cases infections caused by tubercle bacilli and by the various pyogenic cocci remain local, due in most cases probably to low degree of virulence of the infecting organisms, more exceptionally perhaps to well marked immunity of the infected person. While the bacillus of diphtheria and the cholera vibrio remain in a sense local, the latter never entering the circulation and the former exceptionally, both show marked powers to extend by continuity along the mucous membranes upon which they customarily cause their respective infections.

Infectious organisms may be disseminated in the body by continuous extension of the infectious process, as in the successive invasion of the whole respiratory tract by the influenza bacillus, in the spread of erysipelas, etc. The majority of infectious bacteria are capable of this form of dissemination. Microörganisms are also disseminated by metastasis, by which is meant the establishment of more or less far spread secondary foci from a primary focus as the chief centre of distribution. In metastasis by the blood, secondary localizations occur in different organs, as in the abscesses of pyæmia. Tuberculosis, leprosy, syphilis, glanders, pest, blastomycosis, pneumococcal and pyogenic processes, furnish good examples of circulatory metastasis. Lymphatic metastasis is of frequent occurrence, the primary lesion being often located in the skin or mucous membranes. Upon mucous membranes mechanical factors may convey infectious material from established lesions to new points of infection, as in aspiration pneumonias.

The factors that determine the invasion of the blood, especially by the organisms that do so only occasionally (streptococci, gonococci, staphylococci), are not clearly understood, but virulence or pathogenicity—*i. e.*, the power to resist and overcome the phagocytic and other bactericidal powers of the blood—undoubtedly plays a most important role. The resistance of the body must also be considered. Both the bacterial virulence and the resistance of the body are variable conditions made up of a number of complex factors that are as yet difficult or impossible to analyse in a given case. As microbes are distributed in the body there is seen on the part of some a distinct preference for certain tissues. Thus the lepra bacilli seek out the nerves and nervous tissues; the virus of hydrophobia has a special predilection for the nervous system; gonococci tend to localize especially in the joints; meningococci thrive best in the leptomeninges; etc. The reasons for this affinity can be surmised only to depend on subtle chemical attractions between constituents in the microbes and the cells.

THE ELIMINATION OF INFECTIOUS MICROBES AND MICROBIC LATENCY AFTER INFECTIONS.

Accurate knowledge of the ways in which the causative agents of infectious diseases are discharged from the infected body is of great practical value in the application of intelligent measures to render persons with communicable diseases or their agents harmless to other persons. As pointed out by Theobald Smith, the mechanism of elimination is of vital importance to pathogenic microbes in enabling them to continue their life-cycle in new hosts. It may assume many forms that appear well adapted to perpetuate the parasitic species. There are two distinctly different methods: (1) immediate elimination from the morbid focus by way of pathological products; and (2) indirect elimination by means of the circulating blood through normal secretions and excretions; or as in the case of some protozoa with highly specialized avenues of entry and escape, through the body of some insect.

In direct elimination the seat of disease must communicate with the outside of the body. This is the case in all diseases associated with surface inflammation or infection of mucous membranes as an essential manifestation. Here the places of entry, multiplication, and exit, often coincide. Examples are seen in the infectious forms of conjunctivitis; infections of

the nasal mucous membranes (lepra, glanders, diphtheria); of the tonsils and pharynx (diphtheria, scarlet fever); of the laryngeal and bronchial (pulmonary) membranes (tuberculosis, pneumonia, influenza, and whooping-cough); of the intestinal tract (tuberculosis, typhoid fever, dysentery, and cholera); of the genito-urinary passages (gonorrhœa, syphilis, and tuberculosis). In this class belong also local and general infections associated with lesions in the skin (tuberculosis, suppurations, blastomycosis, syphilis, smallpox, measles and scarlet fever).

Unquestionably, cleansing of the mucous membranes (especially of the respiratory and oropharyngeal), and of the materials which they convey, is one of the great problems in the prevention of infectious diseases. Disinfection of the discharges from the urinary and intestinal tracts is a simple matter compared to the disinfection of the sputum, visible and invisible, by practical and generally applicable methods in all these conditions in which it may contain virulently active infectious agents.

In the process of elimination of pathogenic bacteria, especially from remotely situated localities, there is danger of auto-infection, local as well as general, as illustrated especially well by tuberculosis.

In the second (indirect) form of microbic elimination two conditions have to be met: the microbes must reach the general circulation, and they must pass the epithelial barriers of glandular organs and mucous membranes. Infectious bacteria frequently reach the circulating blood often in an accidental and more or less passive manner, but also as the result of inherent invasive powers as in the bacillæmia of typhoid fever and pest, in the pneumococcæmia of pneumonia, and in the active bacteriæmia in virulent, so-called septic infections. Bacteria that enter the blood may be destroyed by its bacteriolytic power; if but few in number and devoid of virulence they may be deposited like inorganic particles in the pulp of the spleen or in the bone marrow and gradually destroyed; and they may be eliminated in the urine, and otherwise. It appears to be generally accepted that some form of lesion is necessary in the kidney in order that bacteria may pass from the blood to the urine. The dangers of spreading infection by this method must be prevented as far as possible. Bacteria are also eliminated from the circulation by way of the bile, and, experimentally at least, certain bacteria are eliminated by the intestinal mucous membrane. As regards the elimination of bacteria from the blood by the glands of the skin, investigations have given contradictory results. Tubercle bacilli frequently occur in the milk of cows with but limited tuberculous lesions not necessarily located in the udder. Tubercle bacilli have been demonstrated in the milk of a woman with advanced phthisis. The unknown causative agent of rabies is eliminated freely in the salivary secretions, which explains the infectiousness of the bites of rabid animals.

Not infrequently some time after an attack of certain acute infectious diseases, as typhoid fever, localized inflammatory processes develop in which are found the bacteria that caused the original infection. A variable period of latency may intervene between the general disease and the localized process. This survival of bacteria is difficult to explain, especially as the patients concerned must be regarded, in a measure at least, as immunized. A somewhat analogous condition frequently obtains in diphtheria, in that more or less virulent bacilli may persist, sometimes for months, in an active condition in the throats and noses of persons who have recovered from

acute attacks. Perhaps recurrent attacks of erysipelas, of acute articular rheumatism, and of other diseases, are caused by the survival in the tissues of the causative agents, awaiting some specially favorable moment, or the entrance of some entirely new factor, to manifest again their original activity. Malaria also furnishes striking examples of latency in the infected host.

Mention may be made of the interesting theories of Baumgarten and Behring in regard to the role of latent tubercle bacilli which, entering the body early in life, are assumed to remain inactive for years before occasion suitable for pathogenic action arises. According to Baumgarten the original infection may be intra-uterine; according to Behring it is alimentary, from cow's milk, the bacilli entering by the digestive tract. Neither theory seems to have a very broad basis of observation or experiment; but the clinical history of the localizations of tuberculosis in man furnishes many examples of the latency and persistence of the bacillus, and the recent studies of old apparently healed tuberculous foci have shown many instances of encapsulated bacilli still capable of causing active tuberculosis, at least in animals. Recently Harbitz has demonstrated the presence of latent tubercle bacilli virulent for guinea-pigs, in the lymph nodes of children, the nodes being normal in structure so far as could be determined.

In immunized animals survival of bacteria also occurs (streptococci, etc.). Tizzoni and Panichi have found that virulent pneumococci injected in otherwise fatal doses into animals, either actively immunized or protected by antipneumococcic serum, may remain alive but inactive in the circulation for weeks and months. According to Panichi staphylococci may be present in the blood in a latent state for some time after the subsidence of local staphylococcus infections. The influenza bacillus, which sometimes causes pandemics of the disease, appears in the interim to exist on the respiratory mucous membranes as a harmless parasite that now and then acts as a secondary invader. It has been suggested that certain infective bacteria may pass into a latent stage in which they are protected against destructive influences at the same time as pathogenic activity is suspended, and that invasive organisms in their evolution toward more perfect parasitism act on the defensive in order to secure opportunity to pass to new hosts. In general, protozoal parasites tend to persist in the blood of the host for a long time even after immunity is established.

MICROBIC ASSOCIATIONS—MIXED AND SECONDARY INFECTIONS.

In the concrete case it may be difficult to distinguish between mixed and secondary infections; but, speaking strictly, mixed infection should mean the simultaneous entrance into the tissues of the body of two or more different virulent pathogenic organisms. It is most commonly observed in the case of local infections of tissues that stand in immediate communication with some of the surfaces of the body which always harbor various bacterial species. In pharyngeal diphtheria, for instance, streptococci enter the tissues of the tonsil so constantly and so early that Baumgarten and others regard this form of mixed infection as constant. Analogous conditions are presented by scarlet fever. Bronchopneumonia due to respiratory infection is commonly probably a mixed infection, pneumococci, encapsulated

bacilli, influenza-like bacilli, staphylococci, and streptococci being associated in all possible combinations. Wound infections are also frequently mixed infections; infections with anaërobic organisms like the gas bacillus, the fusiform bacilli, tetanus bacillus, are usually mixed infections, one or more of the common pyogenic species being present also.

A secondary infection means the occurrence of a second microbic invasion in a body already the seat of an existing or primary infection. In most cases there is good evidence that the primary infection prepares the way and opens the door for the secondary invaders. Thus all primary infections associated with destructive and ulcerative lesions of skin or mucous membranes, like diphtheria, variola, typhoid fever, tuberculosis, etc., facilitate directly secondary infection with microbes, the most important of which normally are present on the surfaces of the body (streptococci, pneumococci, staphylococci, etc.). More than this, we have the best of reasons to believe that infectious diseases, like those just mentioned, directly or indirectly may lead to diminution in the normal powers of the body to resist infections. Smallpox, scarlet fever, measles, tuberculosis, diphtheria, are associated so commonly with secondary infections, especially streptococcal, that there is no escape from the conclusion that the conditions must be more favorable for streptococcal infections in these diseases than in health.

Various groupings of associated infections are possible upon the basis of the distribution and fate in the body of the microbic forms.

1. The associated microbes may remain localized; *e. g.*, in mixed local infections.

2. Both primary and secondary invaders become disseminated more or less extensively throughout the body; *e. g.*, tubercle bacilli and streptococci.

3. The primary organism remains localized or undergoes involution, whereas the secondary invaders persist and extend. A good illustration is general streptococcæmia secondary to diphtheria, scarlet fever, smallpox, measles, tuberculosis, or cholera. Not infrequently this streptococcæmia becomes apparent after the subsidence of the main symptoms of the primary disease. In pneumonia, typhoid fever, influenza, and other diseases, secondary lesions, often of a metastatic character and due to mixed and secondary invaders, may develop after the primary infection has died out.

4. The mixed or secondary invaders remain localized, whereas the chief organism is disseminated. This, the largest group, is illustrated by local suppurative infections in almost all infectious diseases, by the superficial pyogenic invasion of tuberculous cavities, the deeper extension being purely tuberculous, etc.

Manifestly the forms of bacterial association are so manifold that many escape mention in summaries of a general character. A secondary infection may be multiple or mixed, and examples are not wanting of the occurrence of mixed or secondary bacterial infections in protozoan diseases, and *vice versa*.

Association of pathogenic bacteria in mixed and secondary infections tends to increase the danger to the patient. In human pathology we have no positive knowledge of one infection being antagonistic to any other infection. Judging from experiments it seems more likely that the bacterial associations tend to increase the virulence of one or other of the associated bacteria. Roux and Yersin came to the conclusion that the simultaneous infection of diphtheria bacilli and streptococci results in an increased virulence of the

diphtheria bacillus; v. Dungern, on the other hand, concluded that the virulence of the streptococcus was heightened. Experimental tuberculosis assumes a more acute form in the presence of pyogenic bacteria (Baumgarten, Pawlowsky); this is in harmony with the fact that in human tuberculosis fresh eruptions of tubercles appear to follow secondary infections. The change that occurs in many infectious diseases with the advent of secondary severe streptococcus infections, for instance, is an ominous one. Here the effects of the secondary infection are often so overwhelming that, as sometimes seen in diphtheria, the treatment of the primary infection with specific serum may be of no appreciable avail. The beneficial results sometimes observed from the use of yeast cultures in the treatment of furunculosis, gonorrhœa, etc., are not explainable as the result of a secondary infection, because the yeast organisms in these instances are not infective; the results are most likely due to the leukocytosis induced by the nucleinic acid of the yeast.

TOXINS, ENDOTOXINS, BACTERIOPROTEINS.

At the present time the pathogenic effects of infectious microbes are regarded as chemical rather than mechanical in nature. In a few diseases in which there is great multiplication of the infectious agents in the blood, mechanical effects may play some role; and in pyæmia infectious embolism is of great importance; but only a few of the results of infections can be explained on mechanical grounds. Since the discovery by Roux and Yersin of the specific poison of the diphtheria bacillus in 1888, followed soon by Kitasato's discovery of tetanus toxin, the intoxication by bacterial products has been accepted generally as the real explanation of the changes that occur in the infected body. To a certain extent the period of incubation may be regarded as indicating the velocity of the chemical reactions that follow infections. Specific poisons have not been discovered for many of our infectious organisms as they grow in artificial media, and this is explained by many as due at least in part to the profound differences in the conditions about the bacteria when growing artificially and in the animal body. As yet we have no simple reagents to show the presence of toxins and other microbic poisons. This is demonstrated by animal or biological experiments largely, and it is in the cases of certain toxins with characteristic effects, such as diphtheria toxin and tetanus toxin, that investigation has made most progress.

At first there was considerable confusion as to the significance of the word toxin, but gradually it has acquired quite definite limitations, although it must be said that commonly it is used in a very loose way. Toxins in the strict sense are soluble products of bacterial, vegetable, and animal origin (bacteriotoxins, phytotoxins, zoötoxins). Toxins are of unknown chemical structure, sensitive to various influences, especially heat, of high toxicity, the toxic effects becoming apparent after a period of latency or incubation, and in the susceptible animal body they give rise to the formation of specific antitoxins which neutralize each the corresponding toxin in vivo as well as in vitro. Toxins present many points of similarity with organic ferments. Both are very sensitive, labile substances of unknown nature. The idea that toxins in reality are ferments has been strengthened by the demonstration by Morgenroth and others that certain ferments, when

injected into suitable animals, give rise to specific antiferments. The question whether toxins are colloidal substances has not been determined. The most important bacteriotoxins so far known are diphtheria and tetanus toxins, which are well-defined poisons and by themselves alone reproduce with great completeness the clinical picture of the disease caused by the respective mother cells. B. botulinus, B. dysenteriæ, B. pyocyaneus, Staphylococcus albus and aureus, streptococcus, pneumococcus,[1] and other bacteria, also produce true toxins of pathogenic importance; but some of these have only a limited range of activity, *e.g.* the laking of red blood corpuscles (bacterial hæmolysins). Some bacteria produce more than one true toxin; the tetanus bacillus produces tetanospasmin and tetanolysin; staphylococci produce a hæmolytic and a leukocidal toxin, etc.

Ricin, abrin, robin, and krotin, are the phytotoxins which in the hands of Ehrlich were the means of experiments that gave us the foundation of our knowledge of the relations of toxins and antitoxins. Of practical importance are the toxins of pollens which are believed to be the cause of hay fever, in the treatment of which an antitoxin has been introduced by Dunbar. Powerful toxins occur also in the venoms and secretions of snakes and other poisonous animals. In all these cases the true toxin nature of the substances has been established by the production of specific antitoxin.

That bacterial toxins circulate in the blood in some infectious diseases has been demonstrated conclusively many times. Thus Brieger produced tetanus in animals by means of a substance extracted from the amputated arm of a tetanus patient, and Nissen found that 0.3 cc. of sterile serum from a tetanus patient caused fatal tetanus in mice. Wassermann and others have demonstrated the presence in the blood and organs of animals and human beings, dead of diphtheria, substances that in guinea-pigs produce all the lesions peculiar to diphtheria toxin. The hæmolytic toxin of streptococci (streptolysin) occurs in the blood in severe streptococcus infections. In other infectious diseases the effort to demonstrate specific poisons in the blood has not met with much success. But the presence of toxins in the blood does not explain their action, because in animals immune to tetanus, tetanus toxin may circulate in the blood without any damage. And in susceptible animals tetanus toxin is quickly removed from the blood by the nervous tissues, which Wassermann and Takaki found take up tetanus toxin with avidity outside of the body as well. It is now generally accepted in accord with Ehrlich's theory that toxic action of bacterial and other toxins is dependent on chemical union of the toxin with certain cells.

In the case of many infectious bacteria it is believed by many that pathogenic substances are attached firmly to the bacterial cells. At all events soluble poisons do not diffuse to any extent into the culture fluids, and purely toxic effects, independent of actual infection, are obtainable in animals by the use of the dead germ substance or rather crude products thereof. These poisons are called endotoxins, and in infections are assumed to be set free as the bacteria are destroyed in the host by bacteriolytic substances and other means. Not satisfied with this doctrine of endotoxins,

[1] Cassagrandi (*Biol. Centralbl.*, 1903, 1, 200) reports that certain races of pneumococcus produce a hæmolytic toxin. Helly (*Centralbl. f. Bakt*, 1905, xxxix, p. 95) finds that staphylococci, pneumococci, and diphtheria bacilli, produce different toxins for leukocytes.

Welch advanced the theory that the bacteria in this general group give rise in the infected body to toxic substances of the nature of amboceptors.

Vaughan has suggested that in the infected body chemical reactions causing grave injury to cells may take place between cellular and bacterial molecules, toxic groups being withdrawn from the bacteria without necessarily fatal injury. He has studied the chemical composition of bacteria, especially of the colon, typhoid, and anthrax bacilli, and with his pupils has succeeded in splitting off from the bacterial bodies various chemical bodies or groups such as (in case of the colon bacillus) the nuclein, the carbohydrate, the toxic, and the hæmolytic. Whether the toxic bodies isolated in this way are the active pathogenic agents of the organisms in question, and whether they are true toxins in the sense that they will produce specific antitoxins, must be regarded as unsettled problems. Vaughan states that "the colon toxin immunizes guinea-pigs against both itself and the living germ, but with the other organisms experiments have not been carried far enough to justify statement one way or the other." In view of the fact that so many definite bodies can be split off along what seems to be fixed lines of cleavage, Vaughan regards the bacterial cell as a compound of various chemical groups.

NATURAL RESISTANCE AND MICROBIC VIRULENCE.

In order that infection may take place, certain conditions are necessary that permit the specific cause to gain entrance into the tissues, there to exercise its pathogenic powers. In the case of pathogenic bacteria normally present on the surfaces of the body without doing any apparent harm, we assume that the bacteria possess a relatively low degree of virulence or invasiveness and may remain harmless until influences arise that either heighten the virulence or in some way remove or diminish the evident obstacles opposed by the body to microbic invasion. Death is followed almost at once by the invasion of putrefactive bacteria that in life are prevented from entering the tissues. The body also possesses various defensive mechanisms against invasion by pathogenic microbes, and upon the condition of these mechanisms depend the varying degrees of individual resistance (or susceptibility) to the infectious diseases that may attack a given species. Various species show great differences in resistance to infections. Some have apparently absolute natural immunity to certain microbes. Cold-blooded animals in general are immune to bacteria that are infectious for warm-blooded forms. We know of no bacterial disease among cold-blooded animals that is transmissible to man.

Species immunity probably depends largely on the inability of some microbes, parasitic in certain species, to adapt themselves to parasitic life in other species with different chemical and biological qualities, rather than on such differences in resistance as may be accounted for on the score of variations in the general protective mechanisms. In certain species bacterial toxins highly toxic for man, for instance, are without any effect under natural conditions. Tetanospasmin does not produce spasms in amphibians and reptiles, but in certain species this immunity is removed when the temperature is raised by artificial means. Avian tubercle bacilli are able to thrive at a temperature of 43.5° C., at which mammalian tubercle bacilli die. Whether there is true natural immunity of some human races to certain

infectious diseases seems to become more and more doubtful as our knowledge becomes more exact. The alleged immunity of pure Africans to syphilis, once asserted by Livingstone, has been shown to be apparent only and due to lack of opportunity of infection. The different behavior of the same epidemic disease among different races is sometimes explainable by the different modes of living. Again, acquired immunity has been mistaken for natural immunity; Koch showed that the immunity of Ethiopians to malaria is acquired, and the immunity of the natives to yellow fever in districts where the disease is prevalent is probably mostly acquired.

Variations in individual susceptibility, which is always relative, may be due at least in part to variations in local factors, mechanical and chemical, that serve to protect the various surfaces of the body against the entrance of infection. The skin is protective because of its impenetrability to bacteria when intact; the constant desquamation of its superficial layers carries away bacteria vegetating therein; the acid reaction of the perspiration is not favorable to bacterial growth; and the ease with which hyperæmia develops on slight invitation—*e.g.,* scratching—brings to the surface leukocytes and the bactericidal substances in the blood. The peristaltic movements of the stomach and intestines, coughing and sneezing, the flow of urine, epithelial desquamation, and the normal action of ciliated epithelium, are mechanical means of removal of bacteria from various mucous surfaces. The toxin-destroying powers of the digestive juices, the bactericidal effects of gastric juice and other glandular secretions, and the antagonistic action on pathogenic forms of the saprophytes vegetating on mucous membranes, are all protective factors.

As bacteria reach the tissues they at once run counter to the phagocytes and the bactericidal substances (Buchner's "alexins") normally present in the blood even in non-immune persons. Frequently these protective agencies are concentrated about the point of entrance or localization of infectious microbes by inflammatory changes, thereby increasing the local resistance, at the same time as a general leukocytosis may develop. In case some microbes escape into the tissues they are likely to be arrested by the regional lymph nodes and there subjected to similar destructive forces. Normal blood may contain substances that render certain infectious bacteria fit for phagocytosis and others that cause bacteriolysis, and upon the content of the blood in either or both of these substances, capable of acting upon a given infectious bacterium, and upon the number and quality of the leukocytes, may depend the degree of individual resistance to infection by that bacterium. In human beings it has been determined that the normal blood serum causes lysis of typhoid, anthrax, colon, dysentery, cholera, and probably also other bacteria. Phagocytosis also takes part in the destruction of these organisms.

The exact manner in which the antibacterial substances are neutralized, as infections with these bacteria develop, is not clearly understood; it may be that certain particularly resistant bacteria remain unaffected by the antibodies; at all events it is believed that the richer a given blood in the antibody for a particular bacterium the greater the resistance of the corresponding individual. With respect to other bacteria upon which normal serum alone has no direct destructive effect (streptococci, staphylococci, pneumococci, etc.), it is likely, judging from test-tube experiments, that phagocytosis is an important means of protection. The phagocytes require,

however, that the bacteria first must be acted on by substances in the serum—the opsonins of Wright and Douglas—which make the bacterial bodies susceptible of phagocytosis.

Denys, Havet, and Kaisin, were the first to show that intravascular as well as extravascular destruction of streptococci and other bacteria by blood rose and fell with the number of leukocytes. They interpreted this to mean the liberation of bactericidal substances by the leukocytes; but now it seems more likely that such results may depend also on the number of available phagocytes within which the final destruction of the bacteria takes place. At the same time it must be pointed out that Hankin and Kanthack, Buchner, Hahn, Wassermann, and others, have brought forward experimental evidence indicating that bactericidal substances, especially complement (Wassermann), may be derived from leukocytes. The organisms, however, that appear to be destroyed by human phagocytes are not affected by the serum alone, and the origin of the opsonins is yet unknown. In view of the facts that the leukocytes may furnish bacteriolytic complement and that the serum is essential to phagocytosis, the antagonism between Metchnikoff's phagocytic and Buchner's alexin or humoral theories of natural resistance no longer has any basis whatsoever—a fact already long recognized by former partisans—because neither mode of bacterial destruction is accomplished without the conjoint action of the cells and fluids.

It is not safe to make any generalizations as to the relative importance of bacteriolysis and of phagocytosis; the exact nature of the resistance to each pathogenic microbe must be worked out carefully first. The general importance of leukocytosis is shown by the fact that resistance to various infections may be increased in a non-specific manner by the injection into animals of a great variety of substances, all of which have in common the production of an increased leukocytosis, local and general. Distinct but temporary protection against otherwise fatal doses of infectious bacteria may be secured in this way. Serum, blood, various albumins (animal and vegetable), spermin, nucleinic acid, broth, urine, yeast, living and dead bacteria, bacterial substances—*e.g.*, tuberculin, Buchner and Hahn's plasmin—all have been found to act in this manner, and undoubtedly this nonspecific increase in general resistance has been mistaken often for specific effects, especially after the injections of various sera supposed to contain immune antibodies.

Experimentally natural resistance may be diminished by various means. Artificial diabetes renders animals more susceptible to infections than normally; so does diminished alkalinity of the blood; muscular exhaustion has been found to reduce the bactericidal substances in the blood. Reduction of the body temperature renders animals abnormally susceptible to infections. In some of the common human diseases the predisposing causes are of great importance. Diphtheria and pneumonia, the specific causes of which are so widely distributed, are largely cold-weather diseases. The manner in which cold reduces resistance has not yet received a satisfactory explanation. Alcoholism, uræmia, venom intoxication, anæsthesia, exanthematous and other acute and chronic diseases, overcrowding and unhygienic living, all may be said to lower the individual resistance to various infections; but it is not probable that the various factors concerned in these conditions all act in the same way. The hæmolytic and other amboceptors in venoms have a strong affinity for complement, the withdrawal of which

leaves the body open to certain forms of bacterial invasion. Complements and opsonins are neutralized readily by a variety of ions and other substances, such as lactic acid, nucleinic acid, bacterial disintegration products, and proteins and organ extracts have been found to neutralize complements so that it is not difficult to understand how the defenses of the body may become weakened. There are various kinds of leukocytic poisons, also, that may interfere with phagocytosis; but, as yet, the finer analysis of the reduction in general resistance is only in its very beginning.

In infectious diseases complex reciprocal relations are established between the infected and the infecting organisms. The factors concerned may vary on the part of both parties, not only in different species, but also in different individuals of the same species, and from time to time in the same individuals. Various gross conditions may influence the course of infections. We know that experimental infections run the quicker course the greater the number, the more virulent the bacteria introduced, and also as a rule the more directly the bacteria enter the circulation or the large cavities. In this case the natural resistance is so to speak overwhelmed. Hemorrhagic infiltrations, clots, crushed tissue at the point of entrance, favor the development of severe tetanus, pneumococcus, and streptococcus infections, because the germs here have favorable opportunities for growth and increase of virulence. The great influence of the anatomical location of the point of entrance is shown particularly well by streptococcus infections: in the dense and tense connective tissue of the finger it causes a local inflammation in the subcutaneous tissue, phlegmons; in the lymph vessels of the skin, erysipelas; in the peritoneum, peritonitis; in the blood, bacteræmia,—conditions that differ greatly in their course though caused by the same microbe.

In the establishment, progress, and nature of an infectious disease much always depends upon the property of the microbe concerned, which we call virulence. Generally we understand by virulence the degree of pathogenic power of which an infectious organism is capable or possessed. Close analysis reveals that virulence in this sense depends on various properties. It is not necessarily synonymous with invasiveness, because toxicogenic bacteria in the strict sense (B. diphtheriae, B. tetani) possess great toxic power and relatively slight or no invasiveness. In these bacteria virulence depends more on toxicity,—*i.e.*, the production of diffusible, absorbable toxins,—and the body responds by the formation of antitoxins, whereas the production of antibacterial substances is relatively insignificant.

In bacteria in which the disease-producing substances are assumed to be locked up in the cells and set free only as the latter reach the tissues of the body, virulence is necessarily connected with a greater degree of invasiveness. Virulence may be reduced artificially by a number of different methods; *e.g.*, exposure to sunlight, or the addition of chemicals. The virulence of some bacteria may be reduced for one species by repeated passage through members of some other species. The most striking example of permanent loss or modification of virulence is furnished by the virus of smallpox which is reduced to vaccine virus on passage through calves.

As yet we possess no general method for determining the degree of virulence of a given pathogenic bacterium for human beings. High virulence for animals is generally regarded as indicating virulence for man; but Koch and Petruschky found that streptococci of high virulence for rabbits did not cause erysipelas in man, and animal-virulent streptococci occur in normal

throats. The highly virulent bacilli of bovine tuberculosis, so far as we know, seem to have little power of invasiveness in the case of human beings. Vagedes, on the other hand, noted that tubercle bacilli from rapidly fatal cases of human tuberculosis were uniformly specially virulent for rabbits. In practically all pathogenic bacteria, virulence is a variable quantity changeable at the will of the experimenter. As a general rule bacteria are most virulent when taken directly from the animal, and lose virulence, some more rapidly than others, the invasive more rapidly than the toxicogenic, when cultivated on artificial media and removed from "stimulation" by substances from the host. Those media best conserve virulence of certain invasive bacteria that approach closest in comparison to the natural fluids of the body (blood agar, blood serum). Bacteria commonly gain in virulence by successive passages through susceptible animals. Streptococci, pneumococci, typhoid bacilli, cholera spirilla, etc., may be "trained" in this way into a high state of virulence, which they lose again more or less gradually on undisturbed cultivation in the test-tube.

The increase in virulence under these conditions has been explained as the result of survival of the stronger, more resistant elements, whereas the weaker go under. At the same time as this selection of strong, virulent races may be taking place, there is also a good reason to believe that an actual increase in virulence and resistance to the antibodies develops on the part of the bacteria. It has been found that the more virulent certain organisms are, the greater the amount of bactericidal serum necessary to destroy them, showing, as demonstrated clearly by Strong in case of the cholera spirillum, that some highly virulent organisms contain more than the feebly virulent of the substance (receptors) upon which the antibodies must act. Conversely immunization with dead virulent cholera spirilla gives rise to more antibodies and greater protection than immunization with less virulent organisms. Consequently we may conclude that in certain instances at least, but not in all, growth in virulence is associated with increase in the bacterial receptors and in the resistance to antibodies.

Wassermann, Pettersson, and others, have found that in typhoid bacilli virulence is not necessarily associated with increase in receptors. Increase in virulence in streptococci, pneumococci and probably also in other organisms, can, however, not be due to stimulation of receptors of this nature, because these organisms are not destroyed by the serum alone, but by phagocytosis through the intervention of the serum. G. F. Ruediger and the writer have confirmed the observations by Denys and his coworkers, as well as by others, that virulent streptococci are not taken up and destroyed by rabbit leukocytes in normal serum. A virulent streptococcus has been defined in consequence (Marchand) as a streptococcus that is more or less insusceptible to phagocytosis, whatever the reasons may be. Whether increase in virulence on the part of other microörganisms goes hand in hand with insusceptibility to phagocytosis remains to be seen. In the case of the pneumococcus too, the more virulent the strain the greater the insusceptibility to phagocytosis (Rosenow). Deutsch assumes the existence of substances toxic to leukocytes in order to explain bacterial virulence; so far the substances of this kind demonstrated are the leukocidin of staphylococci, of B. suisepticus (Van der Velde), and the leukotoxic substances elaborated by virulent streptococci. The insusceptibility of virulent streptococci and pneumococci to phagocytosis is probably not wholly explainable as due to

leukotoxic substances, because killed and washed virulent cocci are not taken up by normal rabbit leukocytes in normal serum.

Recently Bail has advanced a theory of virulence that is called the "agressin theory." When tubercle bacilli, typhoid bacilli, dysentery bacilli, cholera spirilla, pneumococci, or staphylococci, are injected into animals together with the sterilized exudate produced by infections with the corresponding virulent bacterium, then death follows much more rapidly than when the bacteria alone are infected, and with little or no evidence of phagocytosis by polynuclear leukocytes. Injections of the exudates only have no effect. Bail and his followers assume that in the exudate are certain specific substances that paralyze the phagocytes. Bail believes that he has been able to produce anti-aggressin by immunization with bacterial exudates. Undoubtedly the phenomenon described must be granted. Fehleisen long ago observed that a minute quantity of Staphylococcus aureus mixed with a clear germ-free serum from a spreading cellulitis caused an extensive abscess, whereas the organism injected alone had no such marked effect. Koch also noted that the injection of tubercle bacilli into the peritoneal cavity of tuberculous guinea-pigs caused death rapidly, and an exudate consisting almost wholly of lymphocytes. It is the explanation of the phenomenon to which exception may be taken inasmuch as it does not appear that new specific substances, such as are implied in the word aggressin, have as yet been demonstrated.

Virulence on the part of invasive bacteria means more, however, than increased resistance to bacteriolysis and phagocytosis, because this property alone does not explain wholly the increasing pathogenicity of increasing virulence. If we assume, as is generally done, that the disease producing poisons of typhoid, cholera, pest, and other organisms, are set free on disintegration of the bacterial bodies in the tissues, then increasing resistance to destruction on part of these organisms naturally would tend to result rather in decreasing pathogenicity. Such is not the case. It must be confessed that this is one of the dark places in our knowledge of the nature of bacterial resistance, and resort must be taken in hypothesis. The most comprehensive conception of bacterial virulence is given us in Welch's theory of bacteriogenic poisons. This is an application to pathogenic organisms of Ehrlich's theory of the origin of antibodies in the host. There is "no reason why suitable substances derived from the host may not stimulate parasitic organisms, through a physiological mechanism similar to that operative in cytolytic (bacteriolytic) immunity, to the production of intermediary bodies (amboceptors), which, if provided with requisite affinities, have the power to link complements to cellular constituents of the host, and thereby poison the latter." In other words, why should not constituents from the infected body act upon microbes in the same general way as bacterial constituents act on the cells of the body, and thus set free from the bacteria various poisons for the cells of the body (bacteriogenic antibodies)? This theory, which as yet has not received much experimental verification, explains the well-marked toxic capacities in the infected body, with its wide range of stimulation, of many bacteria that in artificial cultures give little indication of poison-producing powers and quickly lose their virulence.

In view of the fact that microbic virulence rises on experimental passage through a series of more or less resistant animals, the question arises, Why does virulence remain at a comparatively low level in nature? Why are

the mortality rates of infectious diseases falling rather than rising? Theobald Smith answers these questions on the basis of certain general biological considerations. He points out that many pathogenic microbes are reduced more or less completely to a parasitic life; in order that such species may maintain existence they must adapt themselves to conditions that allow invasion of host after host. If such a microbe can not avail itself of some mechanism of transmission it is sure to perish sooner or later. Now the more virulent the microbe the more rapid the death of the host, and the less the chance of escape to new hosts. Consequently there is going on in nature a constant elimination of the most virulent pathogenic microbes in favor of those that are better adapted to parasitic conditions. The degree of permanence of any species depends on the perfection of its adaptation to the surrounding conditions. At the same time there is taking place a gradual weeding out of the most susceptible hosts and consequently a small rise in the average general resistance. The general result of this tendency to advancing parasitism must be decline in virulence and in mortality.

THE CHANGES AND REACTIONS OF INFECTIOUS DISEASES.

The changes and reactions that take place in the animal body in consequence of infections cover a wide field. Here only a brief summary of some of the important general features of the reactions produced by infectious diseases is presented.

Incubation.—This is the period that elapses between the entrance of the microbes and the development of definite disease. In most diseases the length is variable, depending on the amount of infectious material introduced, its virulence, and on the place of entrance; and, on the other hand, upon the relative degree of resistance of the infected body. Experimentally the influence of the amount of infectious material is shown in the case of tetanus; by increasing the quantity of bacilli injected the time of incubation in mice may be shortened from five or six days to twenty-four hours. In rabies and tetanus the period of incubation is as a rule shorter the closer to the central nerve organs the point of entrance. The direct introduction of bacteria into the circulating blood or large serous cavities makes the incubation shorter than after subcutaneous introduction. The influence of bacterial virulence is shown very well experimentally by streptococci, the incubation period being shorter the greater the virulence. In certain human diseases (measles, smallpox, vaccinia) the incubation period is quite constant.

Local Effects of Infectious Agents.—These are essentially necrotic and inflammatory in character. The inflammatory changes may assume varying anatomical forms: serous, fibrinous, suppurative, diphtheritic, hemorrhagic, necrotic, and proliferative. Depending on various conditions, the same microörganisms may cause different forms of inflammation. Thus the streptococcus may cause serous, fibrinous, and suppurative inflammations. In animals different regions of the body respond somewhat differently to the same organisms. In guinea-pigs, diphtheria bacilli and diphtheria toxin cause a serous or hemorrhagic inflammation when introduced subcutaneously, but a membranous exudate when placed on the mucous membrane of the vulva or the trachea. Different animal species also differ in their inflammatory reactions produced by the same cause. There are, however, certain

forms of inflammation that are peculiar to certain microörganisms, as for instance the proliferative inflammations resulting in nodules caused by the tubercle bacillus, the bacillus of glanders, and the organism of syphilis. In this sense miliary tubercles, for instance, are quite specific productions.

The inflammatory changes here discussed are caused by chemical substances of bacterial origin. They are not necessarily dependent upon the presence of living organisms, because the same changes may be obtained by dead bacteria and the sterile products of bacteria. Thus Prudden and Lodenpyl as well as others have shown that the injection of dead tubercle bacilli into the circulation gives rise to tubercles. The sterile diphtheria poison gives rise to the same inflammatory changes as the living cultures. Heber demonstrated that bacteria attract leukocytes, and Buchner that all bacteria contain non-specific proteins that when introduced into warm-blooded animals exert positive chemotaxis upon leukocytes and stimulate the flow of lymph. These proteins, however, do not differ qualitatively, and consequently do not explain the qualitative peculiarities in the various inflammatory reactions, which must depend upon more specific substances produced by or present in the different microörganisms as they multiply in the tissues. As yet these substances are but poorly understood for the most part.

It is accepted generally that the inflammatory reaction, leading as it does to the concentration of leukocytes and serum about the invading microbes, is a measure of protection against general infection. Metchnikoff and his followers have placed special—almost exclusive—stress upon the importance of the phagocytic activity of leukocytes and other cells. Buchner and others have emphasized the role of the bactericidal properties of the fluids. The two views are no longer antagonistic. The phenomena of phagocytosis and of extracellular bacteriolysis in many cases take place side by side, and recent investigations have demonstrated that phagocytosis of bacteria probably does not take place before the bacteria are modified in some obscure manner by substances in the serum (Wright and Douglas's opsonins) at the same time as it is now agreed that some at least of the bodies concerned in bacteriolysis are derived from the leukocytes. It has been shown by v. Dungern and others that there may be a local production of specific antibodies, and it may well be that in this also the inflammatory reaction serves to protect the body at large.

Leukocytosis.—The majority of human infections is associated with a more or less well-marked leukocytosis. Uncomplicated typhoid fever, measles, rötheln, malaria, dengue, uncomplicated tuberculosis except of meninges or serous surfaces, and some forms of general sepsis, constitute exceptions. Inflammatory or infectious leukocytosis is generally an active leukocytosis; *i. e.*, the increase is chiefly in the polymorphonuclear leukocytes, more particularly in the neutrophile forms. The leukocytosis is called active because the cells concerned are mobile, and it is believed that they make their way into the circulation especially from the marrow, which shows increase in the neutrophile myelocytes, by means of amœboid movements in response to positively chemotactic substances. Leukocytes may be produced also by division of existing leukocytes.

Bacterioproteins were regarded by Buchner and Römer as especially active chemotactically because it was found that they caused leukocytosis when injected into animals. Various substances, not all necessarily of

this nature, may induce leukocytosis. In animals infectious leukocytosis is caused experimentally by nearly all pathogenic bacteria or their products; it is commonly preceded by a fall in the number of leukocytes in the peripheral blood of short duration (leukopenia), which is attributed to destruction of cells by the sudden introduction of large quantities of injurious substances. In man, in whom the infections establish themselves more gradually, this initial leukopenia is not nearly so marked or so constant as in animals. By some it is regarded as merely apparent and as explainable by an unequal distribution of the cells, an unusually large number being held back in the capillaries of the internal organs. As the positively chemotactic substances diffuse more uniformly and in greater quantities the leukocytes are distributed more equally. The occurrence of leukopenia in some infectious diseases is explained more easily as due to the presence in the blood of substances that exercise a negative chemotaxis on the leukocytes.

It is generally believed that leukocytosis in infection is beneficial not only because of the phagocytic activity of leukocytes with respect to bacteria as well as to cellular detritus of various sorts, but also because the leukocytes may be the source of bactericidal and antitoxic substances (Metchnikoff and others). Experimentally it can be shown that the destruction of bacteria which are destroyed by phagocytosis (streptococci and pneumococci and human blood), is greater, the greater the number of leukocytes present in the same serum. G. F. Ruediger and the writer have found that the leukocytes in experimentally produced leukocytosis are fully as active phagocytically as those normally present. The increase in general resistance by increasing the number of leukocytes by various substances—nucleinic acid, salt solution, broth serum—points to the value of leukocytosis. Mickulicz and others obtained good effects in surgical operations upon the abdominal organs by first inducing an artificial peritoneal leukocytosis—"preparing the peritoneum."

Effects on Red Corpuscles.—Anæmia is common in infectious diseases, and it is of interest to note that toxins capable of laking red blood corpuscles (hæmolysins) are produced by several pathogenic bacteria. Van de Velde found that staphylococci produce a lysin of this kind; it has been studied fully by Neisser and Wochsberg, and called by them staphylolysin. This substance seems to be produced by all pathogenic staphylococci. Normal human blood contains antilysin, and in staphylococcus infections newly formed antilysin develops in large quantities. Ehrlich and Madsen found a lysin in crude tetanus poison (tetanolysin). Besredka studied the lysin of virulent streptococci (streptolysin), the existence of which has long been indicated in the laking of blood observed after death in cases of "sepsis," and in experimental streptococcus infections. Ewing found in primary hemorrhagic smallpox a hæmoglobinæmia with pigmentary deposits similar to those seen in puerperal streptococcus septicæmia. G. F. Ruediger has found that streptolysin has the constitution of a toxin, but as yet no immune antistreptolysin has been produced, though the serum of different normal animals contains distinct antibodies. Jordan has shown that the hæmolysis of filtrates of pyocyaneus cultures is caused by hydroxylions and probably not by any toxin, as has been claimed.

Bacteria also produce hæmagglutinins (Kraus), and it has been suggested by Flexner that the hyalin thrombi of red cells observed in typhoid fever are caused by the action of such agglutinins. Necrosis in the liver in hog

cholera has been referred to hyalin thrombi by Bosmeyer, and Pearce has produced liver necrosis experimentally by injecting immune hæmagglutinins. That red corpuscles undergo disintegrative changes in many infectious diseases is shown also by the extensive phagocytosis of red corpuscles by hyalin cells (leukocytes and endothelial cells) that occurs in the spleen, the lymph nodes, the hæmolymph glands, and the lymph and bloodvessels in various parts of the circulatory system in typhoid fever, scarlet fever, and other infectious diseases, and which has been studied by Mallory, and by Warthin with special reference to the hæmolymph glands. To what extent isoagglutinins and isohæmopsonins take part in agglutination thrombi and in phagocytosis of erythrocytes in these conditions remains to be seen.

Changes in Blood-making Organs.—Enlargement of the spleen is characteristic of many infectious diseases. This may depend in part upon the lodgment there of degenerated red corpuscles, disintegration of which occurs on a large scale in certain infections. The phagocytic activity of nongranular leukocytes and endothelial cells is often remarkable, and Mallory has suggested that bacterial toxins stimulate the phagocytes. The exact mechanism requires further study with special reference to substances of the nature of opsonins. Jawein found that intoxications with the chlorates of potassium and sodium and with toluylendiamin caused splenic enlargements in correspondence with the destruction of the red cells which were taken up by the cells in the splenic pulp which enlarge and multiply at the same time as hyperæmia develops. Splenic enlargement may also be dependent on an active hyperplasia connected with the formation of specific protective substances, as in typhoid fever (Pfeiffer and Marx). Here the absence of leukocytosis may be compensated so to speak by splenic enlargement. Blumreich and Jacoby found that, experimentally, splenectomy did not decrease the resistance to various infections, possibly because it is followed by a leukocytosis, according to Kurloff, chiefly of lymphocytes.

In infectious diseases the fatty marrow is frequently replaced by lymphoid, in which the neutrophile myelocyte is the chief element. Phagocytic cells, the action of which is directed chiefly toward red corpuscles and leukocytes, also appear. Myelocytes appear in the spleen and also in the blood. Muir questions the occurrence of the so-called myeloid transformation of the spleen claimed by Dominic and other French writers. In the lymph and hæmolymph nodes, endothelial proliferation and phagocytosis are the most striking changes—and, according to Warthin, the destruction of red cells by phagocytosis may be greater in the hæmolymph glands than in the spleen.

Diverse Actions of Microbic Poisons.—The parenchymatous degeneration of the heart, liver, kidneys, and spleen in infectious diseases is probably caused by bacterial poisons, although Litten, Welch, and others, claim from experiments that parenchymatous changes may result from hyperthermia. Naunyn, however, exposed rabbits to high degrees of heat for weeks without demonstrable degeneration. The exact relations of bacterial substances to the formation of amyloid material are somewhat obscure. Focal or insular necrosis occurs in lymph glands, spleen, bone marrow, and parenchymatous organs in many infectious diseases, due to toxic action upon local cell areas.

Many infectious microbes and their poisons show a special affinity for the nervous system. The tetanospasmin unites with constituents in the neurocytes, which it reaches by way of the axones (Meyer and Ransome).

Lepra bacilli have a selective affinity for nervous tissue. The constituent of the crude diphtheria toxin that Ehrlich has called toxon, regularly causes paralysis in rabbits quite like that of peripheral neuritis. The close relations between myelitis and different infectious diseases have given rise to many experiments, the results of which have shown that diverse bacteria and their products—pyocyaneus toxin, typhoid bacillus, colon bacillus, streptococcus, pneumococcus, staphylococcus—may cause grave changes in the spinal cord.

The exact investigations of the influence of bacterial poisons on the functions of the various glands and on the nerves of the circulatory apparatus are as yet only in their beginning. It has been found that the extract of the adrenals of guinea-pigs and rabbits that have died of diphtheria intoxication and various infections have no power to raise the blood pressure. According to Charmin and Gley the pyocyaneus toxin paralyzes the vasodilators. Paessler and Romberg conclude that in experimental pneumococcus, pyocyaneus, and diphtheria infections, vasomotor paralysis is the real cause of the failure of the circulation. Typhoid infection lowers the blood pressure, while staphylococci, streptococci, and colon bacilli, cause it to rise. The toxicity of the urine has been claimed to be greatly increased in infections by Bouchard and his followers, but uniform results have not been obtained, and the entire subject of urotoxic action needs renewed investigation. Roux and Yersin found diphtheria toxin in the urine of diphtheria patients, and Bruschellini tetanotoxin in the urine of patients suffering from tetanus.

Fever.—Fever is usually present at some time or other in the course of all infectious diseases. While its causes and nature vary greatly in different infections there seems no doubt that the presence in the body of active infectious material as a rule causes fever. The introduction under the skin in susceptible individuals, of a small amount of dead virulent bacteria as in various protective inoculations, is practically always followed by a more or less distinct febrile reaction. Under these circumstances there is no doubt that fever is caused by the absorption of chemical bacterial products. In the case of animals, especially guinea-pigs, bacterial substances in small doses cause a rise of temperature, but in large doses fall of temperature with collapse may result.

Numerous experiments have been made to isolate the fever-producing substance in bacteria. Buchner found that his bacterioproteins cause fever in both man and animals. Matthes regards albumoses as the cause of fever. Centanni's pyrotoxin is a substance, soluble in water and insoluble in alcohol, without proteid reactions, which he obtained from fluid cultures of all kinds of bacteria. Krehl points out that special stress cannot be laid on these particular substances because almost all albuminous derivatives of protoplasm cause some rise of temperature when injected in animals. Whether the substances mentioned as well as other eventual pyrogenic bodies act directly as such or indirectly by first causing special fever-producing bodies to be formed from the constituents of the infected organism, is an open question. The experiments to demonstrate pyrogenic substances in the blood of feverish animals have given contradictory results so far.

While substances like pyrotoxin and bacterioproteins no doubt cause fever in animals, the many definite types of fever curves in man indicate that there is no single thermogenic substance which is common to all in-

fectious microbes and causes all fevers. Experimental animal fever so far has failed to show the peculiar cycles of fever in man that point to more specific reactions. The fever type is clearly associated also with the production of specific antimicrobic substances. In recurrent fever the fall in temperature has been shown by Gabritschewsky to be associated with the appearance of antibacterial substances that check the development of the spirilla. As these substances diminish a new attack sets in. There is reason to believe that the fall of temperature with the crisis in pneumonia depends on the somewhat sudden development of pneumococcidal and other reactions because the pneumococci as a rule disappear from the circulating blood as crisis comes on. In cholera and typhoid the protective substances develop gradually, in the spleen especially, and here the fever terminates by lysis.

Special peculiarities are shown also in the production of fever in the tuberculous by the injection of tuberculin, and in lepers by potassium iodide. At the same time more or less fever may be caused in infections by substances of a more common character; it is, for instance, quite likely that disintegration of red corpuscles may set free pyrogenic substances. The chill, characteristic of the onset of many infectious diseases, is thought to be caused by spasm of the cutaneous nerves under the influence of toxic bacterial products. Working Party No. 2 of the Yellow Fever Institute at Washington found that filtered blood withdrawn at the time of the malarial chill produces a chill on intravenous injection.

From animal as well as human experiments we know that the cellular reactions that lead to the production of specific antibodies—antitoxins, lysins, agglutinins—often are all associated with fever. When excessive quantities of antigenic substances are injected there may be fall of temperature in place of rise, as well as general collapse, and the absence of fever in severe infections may be an indication that the cells are so overwhelmed that they cannot react in the usual way. Viewed in this light, fever in infections may be regarded as an indication that the production of antibodies is progressing favorably.

For centuries fever was regarded as the expression of an effort on the part of the body to overcome the cause of the fever. Liebermeister was the first to break with this conception and to hold that the pyrexia of fever is in itself harmful. At present there is a tendency to regard fever as beneficial at least in infections, rather than harmful. Various experiments have been made to determine the influence of pyrexia on infection, but it seems rather doubtful whether the results are applicable to fever in human diseases. The fact that a temperature of 41.2° C. is injurious to certain bacteria in artificial culture loses a great deal of significance as regards the effect of similar temperatures in an infected body, because the conditions in vivo and in vitro are so different. It has been found that rabbits kept in a warm chamber (41.2° C.) or rendered hyperthermic by injuries to the nervous system withstand various infections better than control animals under the usual conditions. This effect was obtained, however, only when the pyrexia was induced at the same time or very soon after the infectious organisms were introduced into the body—*i. e.*, during the incubation period—and hence may have been due to some increase in the general resistance (leukocytosis?), while in spontaneous human infections fever develops at the end of the incubation period when the infection is duly established. It is therefore doubtful whether these experiments really mean anything as regards the effect of fever on spontaneous infections.

The Effect of Infectious Diseases on Metabolism.[1]—Microbic infection may produce chemical changes in the human body in three main ways: First, by changing, either chemically or in amount, the substances entering the body; second, by altering in the same manner the substances leaving the body; and third, by setting up new chemical processes in the tissues themselves. The amount of substance taken into the body through the gastro-intestinal tract may be reduced in infectious diseases in many ways; as by anorexia, by pain (as in infections of the pharynx and buccal cavity), by muscular inability (as in the spasms of tetanus), or by lack of nervous control (as in delirium). The available material may be further lessened, by vomiting, by diarrhœa, by diminished power of the digestive juices, or by a direct interference with intestinal absorption. This latter may be caused by excessive mucus, by exudates, by œdema, or by intestinal anæmia, which interferes because the main avenue of absorption is through the smaller bloodvessels.

In whichever way the diminution in intake is brought about, characteristic chemical changes result, which approximate, to a greater or less degree, those of inanition. The life processes are then necessarily maintained at the expense of material already stored in the body. A rapid and ultimately an almost complete consumption of carbohydrates and fats occurs, and a gradual reduction in the proteids, which reduction is greatly accelerated as soon as the fats and carbohydrates have reached a minimum. These chemical changes bring about alterations in the output from the body, especially in the expired air, and in the urine. The respiratory changes depend on changes in the kind of material oxidized. As soon as food is withheld and the carbohydrates and fats of the body are in large part consumed, the patient is practically living on a pure proteid diet—the proteids of his own tissues. The respiratory co-efficient, that is, the ratio between expired carbon dioxide and consumed oxygen, therefore, rapidly decreases from 0.85, its value on an ordinary mixed diet, to approximately 0.7, its value on a pure proteid diet.

The most important urinary changes are those of nitrogenous excretion. Following the cessation of intake of food, there is a rapid drop in the amount of N excreted, which continues until a minimum is reached, representing the smallest proteid destruction compatible with life. The body is now living almost entirely on stored-up non-proteid material. As soon as this is exhausted, it begins to draw upon its proteid, when generally a sudden increase takes place in the amount of N excreted. Some interesting changes also take place in the excretion of inorganic salts. Thus the sulphates and other sulphur-containing bodies run roughly parallel in their variations with the changes in nitrogen. The chlorides probably undergo more marked changes than the other inorganic substances. In the body an attempt is apparently made to keep the amount of NaCl constant, so that practically all NaCl taken with the food promptly appears in the urine. On withdrawing food, this source of NaCl is therefore cut off. The excretion then represents only the small amount of NaCl set free by tissue destruction. The tissues themselves contain a relatively large amount of potassium, but only a small amount of sodium, the ratio being about 3 to 1. The food, however, usually contains an excess of sodium, due mainly to the NaCl added in its prepa-

[1]For this section I am indebted to W. H. Manwarring, M. D.—L. Hektoen

ration. On withdrawing food, therefore, one would expect, not only a marked decrease in the absolute amount of potassium and sodium excreted, but a marked change in their relative proportions. This is found to be the case. While normally potassium and sodium are excreted in the approximate ratio 2 to 3, which represents roughly the K-Na ratio of ordinary mixed diet, in inanition this ratio rapidly increases, and eventually becomes 3 to 1, the K-Na ratio of living tissue. A similar change takes place in the excretion of calcium and magnesium. The Ca-Mg ratio on an ordinary diet is generally less than 1; but it increases and becomes greater than 1, as soon as the body commences to live on its own substances.

Infectious diseases may further interfere with the intake of material by producing changes in the respiratory tract. The amount of oxygen entering the tissues may be reduced by a narrowing of the respiratory passages (as from œdema), by an interference with respiratory movements (as from pain), by an interfering with the passage of oxygen through the alveolar walls (as from the presence of exudate), or by a reduction in the oxygen-carrying power of the circulating fluid (as in severe anæmias). The resulting alterations in chemical activity must be pronounced, but their exact nature is poorly understood. Their general character is indicated by the increase in the urine of oxalic acid, lactic acid, ammonium salts, xanthin bases, and other products of incomplete oxidation.

Infectious diseases may alter the chemical composition of substances ingested. This is most marked in the gastro-intestinal tract, and may be brought about either by abnormal chemical changes in the material ingested or by abnormal absorption or synthesis of the digestive products. Abnormal chemical changes in the ingested material usually result from the excessive action of yeasts and putrefactive bacteria, but they may result from the action of specific microörganisms as well. Lowered acidity of the gastric juice, and lessened peristalsis, which characterize so many infections, both favor microbic growth. Fortunately most products of decomposition so irritate the mucosa that vomiting and excessive peristalsis result. The absorption, however, is usually sufficient to set up marked metabolic changes. Such substances as CO_2, H_2S, cadaverin and putrescin, so absorbed are in large part excreted unchanged. Most of the acids so absorbed unite promptly with the alkalis of the body fluids, forming alkali salts, in which form some of them may appear in the urine. Phenol, kresol, and certain aromatic oxyacids, unite directly with potassium, hydrogen sulphate, glycocoll, and glycuronic acid, to form stable, nontoxic conjugation products, which are excreted unchanged in the urine. Others, as indol and skatol, are first partly oxidized to indoxyl and skatoxyl, which then form conjugation products; others as tyrosin, are completely oxidized in the tissues.

Not only may infection alter the intake of material through abnormal putrefactive processes, but it probably may do so by altering intestinal absorption as well. It is possible that local changes may so modify the intestinal mucosa that substances not normally taken up are absorbed, and substances normally absorbed rejected. There may also be alterations in the intake of material by interference with the synthetic process. The nature of these changes is as yet largely a matter of conjecture.

Interference with the output from the body may bring about abnormal retention of products usually excreted. Such retention may result from alterations in the excreting organs, or may occur with apparently no change

in the excreting organs themselves, as seen in the retention of chlorides, phosphates, and other salts in acute fevers. This is believed to be a measure designed to preserve the normal osmotic relations in the body altered by the destruction of circulating proteid. Retention may also take place in infectious diseases like pneumonia, in which there is the formation of large amounts of exudate. In whichever way it is brought about, an accumulation of waste products, normally present only in traces, results, and the compensatory throwing out of these products by unusual routes.

The infectious diseases may on the other hand cause abnormal losses. Thus in inflammatory diseases of the kidney, or in slight alterations of renal epithelium due to toxins, there may be a considerable loss of albumins. globulins, and other blood constituents. In diarrhœa there is often so great a loss of water as to lead to a real desiccation of the tissues, as in cholera. Here there is also loss of large quantities of albuminous material, Marked loss of blood may occur, as in the intestinal hemorrhage of typhoid fever, the pulmonary hemorrhage of tuberculosis, etc. The most marked losses, however, probably occur through the discharge from the body of inflammatory exudates and necrotic material. Losses, from whatever cause, produce marked quantitative changes in the amount of albuminous and other material of the body fluids. Indirectly they bring about qualitative changes as well, as they affect the body in practically the same way as inanition, bringing about further changes in the respiratory quotient, nitrogenous excretion, and K-Na co-efficient.

There are equally marked changes due to alterations in the chemical processes within the body itself. These may be due (*a*) to modifications of function; (*b*) to increase in katabolism in the tissues as a whole; (*c*) to increase in temperature; or (*d*) to tissue destruction. Alterations in function, outside of those in the glandular organs discharging on the surface of the body, are poorly understood. But the marked changes in the gastric juice, the increased viscosity of the bile, the suppressed or increased amount of sweat, and the modifications of the urine and mammary secretions, indicate that probably all of the tissues of the body are profoundly affected in their metabolic activity, either through the direct action of toxic substances or waste products, or indirectly through nervous, circulatory, and respiratory changes. Outside of these there are numerous changes of a more general nature that can be classed under the head of increased katabolism. This shows itself not only in the increased heat production, but in the appearance in the excretions of an increased amount of all of the end-products of metabolism. Nitrogenous excretion is increased two or three times that of a normal man on the same diet, and the K-Na co-efficient is still further altered by the increased liberation of the potassium of the tissues.

Infection may cause death and disintegration of certain cells of the body and the decomposition of body fluids. This is illustrated by the breaking down of the erythrocytes in malarial fever, by the destruction of the capillary endothelium in severe exanthemata, by parenchymatous degeneration, and by the circumscribed necrosis of abscesses. The effect of this destruction depends largely on whether or not the dead tissue is invaded by micro-organisms. If not invaded, a comparatively slow autolysis occurs, due to intracellular and circulating enzymes, with the formation of albumoses and smaller quantities of peptones and other end-products of tryptic digestion. If bacteria enter there is in addition a rapid putrefactive process,

giving rise to decomposition products similar to those of intestinal putrefaction. Among these are histone, Bence-Jones albumose, and certain diazo bodies. Certain of these products, as the hæmoglobin set free in blood destruction, may appear unchanged in the urine. The other substances undergo changes similar to those in intestinal putrefaction.

It is probable also that there are profound changes in delicate proteid molecules due to changes in temperature alone. When we consider the marked changes in the ionization of simple salts, and in the arrangement of atomic groups in simple organic compounds, that follow an increase of only a few degrees in temperature, it is clear that there must be innumerable similar changes in tissue molecules due to the same cause. What these changes are is yet a matter of hypothesis. Theoretically one would expect an increased dissociation of complex substances, a rearrangement of simpler radicals, and a hastening of all processes depending on ionization. The fever, therefore, would tend to increase in the body the formation of end-products of tissue metabolism.

Considering the chemical processes of infectious diseases as a whole, one is struck by the prominent role played in these diseases by the products of proteid decomposition. One sees how much the medicine of the future depends on an increase in knowledge of these products. When one considers that, in many diseases, the harmful effects are due as much to the action of these substances as to the direct action of the bacteria themselves, the possibility of assisting the organism, in some direct manner, to neutralize these products, or to inhibit the action of the enzymes that gives rise to them, is suggested.

The Formation of Antibodies.—Most important reactions in infections are those that result in the recently discovered antibodies, the general action of which is to neutralize morbific microbic products and destroy the invading microbes. For centuries it has been a matter of common knowledge that recovery from an infectious disease leaves behind a more or less well-marked immunity to that disease, and this we now know is intimately associated with these cellular reactions. The bodies concerned are the antitoxins, the amboceptors, the agglutinins, the precipitins, and the opsonins. Our knowledge of immunity—natural and acquired—and of the reactions whereby antibodies are produced, is inseparably connected with that of modern protective and therapeutic inoculation and serum therapy.

IMMUNITY, ANTIBODIES, AND SERUM THERAPY.

Introduction.—The development of immunity is the natural termination of many acute infectious diseases, provided, of course, that the infection is not so severe as to destroy the mechanism of self-healing. Advantage was taken of this fact in the inoculation of smallpox and later the success of vaccination suggested that possibly infection with attenuated virus in general would give the same protection as with the fully virulent. In 1881 Pasteur successfully vaccinated sheep against anthrax by means of cultures of attenuated anthrax bacilli. The principle of artificial immunization (vaccination, protective inoculation) against diseases of known microbic cause was now established.

The actual beginning of definite studies of the finer mechanism of infectious reactions may be placed in 1888, when Roux and Yersin discovered diphtheria toxin. Then came Behring's discovery, in 1890, of diphtheria antitoxin in the body of animals injected with increasing quantities of diphtheria toxin, and analogous observations with respect to tetanus toxin (Behring and Kitasato), and to the vegetable toxins, ricin and abrin (Ehrlich). The further demonstration was made by Behring that antitoxic serum may protect healthy animals against fatal doses of the corresponding toxin, and even cure those already sick; and curative serum therapy was established. "Thus an innate faculty of the animal organism to develop in a marvelous manner its own resources was turned to the common good."

The expectation that it would be an easy matter to obtain specific sera against all microbic diseases proved illusory because many infectious bacteria do not produce diffusible toxins as do tetanus and diphtheria bacilli. It became established that *acquired antitoxic immunity,* which depends on the chemical neutralization of pathogenic toxin by specific antitoxin, has only a limited range. Many cases of natural immunity to toxins appear to be due to an absolute insusceptibility of the cells of the animals to the action of the toxin, which may, as shown by Metchnikoff in the case of tetanus antitoxin, circulate free in the blood of the immune animals. In other cases immunity may be the result of absorption of the toxin by cells of relatively little importance to the economy, or in which the toxin has little pathogenic power. The chicken has a relatively high immunity to tetanus; it requires 200,000 times more toxin, gram for gram of weight, to kill a chicken than it does a horse; yet chickens contain no tetanus antitoxin.

In many infectious organisms the special poison is held to be firmly attached to the bacterial cells, being freed only as the cells disintegrate or elaborated under the special stimulus of the invaded body. The poisons contained in the cells are called endotoxins, but so far it has not been possible to discover any potent anti-endotoxins. As active immunity becomes established against certain microörganisms of this class, newly formed specific bacteriolytic substances appear in the blood and for this reason the immunity in this case has been regarded as *antibacterial* or *bacteriolytic* in nature. Natural immunity in some cases appears to be associated with bactericidal substances in the blood. Thus white rats are immune to anthrax and their serum is highly destructive of anthrax bacilli. In other cases there seems to be no necessary relation between natural and bactericidal immunity power, as in typhoid fever, which develops in spite of the fact that human serum is strongly bacteriolytic for typhoid bacilli.

Acquired bactericidal immunity may be conceived to depend on the circumstances that the destruction of the bacteria, which it is true takes place also in normal serum, now is hastened so that it is complete before the bacteria present have had the chance to multiply to the extent that a fatal dose of the poison, however produced, is set free. The relative immunity that appears to persist for some time after the specific bacteriolytic substances have disappeared from the blood has been explained as dependent upon an acquired sensitiveness of the cells, which now react with greater promptness and efficiency than before and thus set free on slight stimulus abundant antibodies (Wassermann, Cole).

Certain organisms appear to be destroyed by virtue of serum acting on the bacteria and phagocytosis by leukocytes of bacteria so influenced. Immunity produced in this way may be spoken of as *phagocytic* or *intracellular antibacterial immunity.* The natural immunity of dogs to anthrax is at present best explained as phagocytic.

We are without any explanation of the exact manner in which the endotoxins and other hypothetical poisons are neutralized in the last two forms of immunity, and there are many obscure phases in connection with those infections in which endotoxins are regarded as playing the essential part. It is more than likely that in many infectious diseases, healing and immunity are associated with all the three forms of reaction mentioned, and it is a present problem to determine for individual diseases the exact nature of the mechanism of healing. In all these forms of acquired immunity a distinction is made between active and passive immunity. Active immunity develops as a consequence of the reactions in the course of spontaneous or artificially produced infection. Passive immunity is the result of the introduction into the body of ready-made antibodies, whatever their nature, as in the injection of antidiphtheric serum. Passive immunity is always of shorter duration than the active. At the present time the study of immunity is directed by Ehrlich's lateral chain or receptor theory. In its beginning this was advanced to explain the origin and action of diphtheria antitoxin and to give a basis for its standardization; but it has proved itself applicable to an ever widening range of similar problems.

The Origin of Antitoxins and Other Antibodies.—Bacterial and other toxins have the power when introduced into the susceptible animal body to induce the formation of specific antibodies. All substances with this property may be classed as *antigens.* Ehrlich's conception of the mode of action of antigens is perhaps best illustrated by reference to the action of toxins, the earliest antigens studied. Briefly stated, Ehrlich's theory assumes that a toxin can be harmful only after a chemical union with constituents (side-chains, receptors) in the protein molecules of the cell of proper stereochemical configuration ("as a key fits its lock"), somewhat in the same way as food particles are taken up. If a cell contains no receptors with which a given toxin can unite, then that cell is naturally immune to the toxin. Sachs showed that the red corpuscles of the newly hatched chick are quite insusceptible to spider toxin (arachnolysin), which they do not take up; later, however, cells appear with the proper side-chains or receptors, and now the toxin causes laking. In some animals immune to certain toxins, the latter may remain free and seemingly unchanged for days and weeks. That toxins unite firmly with cells is shown by the firm fixation of tetanus toxin by nerve tissue (Wassermann and Takaki). Dönitz has demonstrated that it concerns here the gray matter, the neurocytes. Numerous other similar examples can be cited.

Like certain complex chemical compounds of known composition, the toxin molecule is regarded as having two distinct atomic groups, one whereby it unites with cell side-chains or receptors, and called the haptophore or binding group, and one by means of which it exercises its peculiar toxic effect, and hence called the toxophore group. In the case of other antigens—*e. g.,* precipitinogen, agglutinogen—the group corresponding to the toxophore group is commonly called the functional group. This conception explains the fact that when toxin and other antigens in general become old,

or are subjected to chemical and other influences, they may weaken in their special toxic or other properties, but nevertheless produce antibodies in suitable animals. Evidently the functional group is the more sensitive, whereas the haptophore group persists and unites with cell receptors. Toxin so changed is called toxoid, and we know of several other "oids"—agglutinoids, amboceptoids, complementoids. In the case of toxins it is possible to separate in point of time the action of the two groups: in frogs tetanus toxin is not toxic below 20° C. in spite of the fact that the toxin is bound to nerve cells below this temperature; only at a higher degree does the toxophore group unfold its activity (Morgenroth).

Now when certain special receptors of a cell are occupied by the haptophore groups of a given antigen to such an extent that it interferes with their function in metabolism, then a regeneration of receptors begins, which, according to Weigert's law of regenerative overcompensation, gives rise to more receptors than the cell needs, and these are thrown off from the cells into the circulation as free antibodies. Wassermann believes that in receptor formation the functional group of the antigen stimulates the cells involved. Any cell that can bind antigens and produce receptors may produce antibodies also. This power is probably widely spread among the cells of the body. Antibodies may form in loco where antigens are deposited, as shown by Römer, who found that treatment of the conjunctiva of one eye with abrin gave rise to antiabrin in that eye only; and by v. Dungern, who found that specific precipitin was formed in the treated eye only, and nowhere else. Kraus and Levaditi secured evidence that precipitin is formed by leukocytes. Wassermann and Citron recently showed that there may be a local production of antityphoid bodies on the part of the cells of the pleura, peritoneum, and possibly of the subcutaneous tissues.

Among free cellular receptors are antitoxins, antiferments, agglutinins, precipitins, and various amboceptors, the nature and function of the particular receptor set free depending on the antigen that by union with fixed-cell receptors stimulated the mechanism of receptor formation (see Table).

ANTIGENS AND ANTIBODIES.

Antigens. (IMMUNIZING SUBSTANCES)	*Antibodies.* (PRODUCTS OF IMMUNIZATION)
Toxins	Antitoxins
Ferments	Antiferments
Precipitinogens	Precipitins
Agglutinogens	Agglutinins
Opsogens	Opsonins
Lysogens (amboceptorgens)	Amboceptors (lysins)
Antitoxins	Antiantitoxins
Agglutinins	Antiagglutinins
Complements	Anticomplements
Opsonins	Antiopsonins ?
Amboceptors	Antiamboceptors
Precipitins	Antiprecipitins

By careful stimulation of this mechanism with gradually increasing quantities of antigen large amounts of antibody may be produced. For a short time after the inoculation of various antigens there ensues a depression of the mechanism of antibody formation ("negative phase") which soon gives way to an active production of antibodies ("positive phase") after which there is a gradual return to the normal. It has been found that re-inoculation

during the negative phase generally serves to prolong and deepen that phase and that the greatest yield of antibodies is obtainable by reinoculation in the positive phase This physiological fact is made use of by Wright in determining the proper time for administering bacterial antigens for therapeutic purposes. It is regarded as a well-established law that animals do not form antibodies against constituents of their own bodies and to a limited extent only against those of closely related species, but there are exceptions to this rule.

Intra-uterine Transmission of Antibodies.—Ehrlich's classical experiments with mice immunized against ricin, abrin, and robin, show exclusively that immunity is not transferred to offspring by way of ovum or spermatozoa. The brief immunity observed in the young of immune mothers is passive in its character and due to transmission of maternal antitoxin through the circulation before birth and in the milk after birth. Analogous results were secured by Ehrlich and Hübener in the case of tetanus, and by Wernicke in the case of diphtheria—immune mothers (guinea-pigs) transmitted an immunity to their young lasting at the very most into the third month. Actively immunized mothers transfer agglutinins (Dieudonne), hæmolytic amboceptors (Kraus), and precipitins (Werkel) to offspring. It has been shown that the eggs of immunized chickens may contain antitoxin.

Antitoxins.—Antitoxins are free cell receptors. They are protective and even curative, because by uniting with the haptophore groups of the toxin molecules they prevent these uniting with the cells. As stated by Behring, the substances in the body that, when situated in the cells, are a primary essential for the toxic process, become curative agents when they enter the blood stream. There are, however, examples of antitoxin production in clinically immune animals. Metchnikoff found that the alligator, which is immune to tetanus, produces antitoxin when injected with tetanus toxin; in this case it is probable that the toxin is bound by cells outside the nervous system upon which the action of the toxophore group has no recognizable clinical effect. Not all animals influenced by a certain toxin respond to small doses of toxin by producing antitoxin. In guinea-pigs and rabbits, for instance, diphtheria and tetanus toxin when unchanged only increases susceptibility. By modifying the toxin with chemicals or in other ways it becomes possible to increase resistance so that increasing doses of toxin may be injected and antitoxin set free.

The sera of immunized animals do not always possess the same curative and protective value. Depending on various complicated factors such as constitution of the animal, duration and degree of immunization, etc., the potency of antisera varies within wide limits. Hence it becomes necessary to establish units for measurements of the strength of sera. Progress in serum therapy depends on the employment of sera of ascertained quality, so that comparable results may be secured. In this country antidiphtheric serum is the only official serum as yet.[1] As regards tetanus antitoxin the

[1] A description of the methods by which the immunity unit for diphtheria antitoxin is obtained is given by M. J. Rosenau, *Bulletin No.* 21, Hygienic Laboratory, United States Public Health and Marine-Hospital Service, Washington, pp. 1–92, 1905. In view of the fact that the standard serum issued by the United States Public Health and Marine-Hospital Service is the official standard for this country, the description of the methods of testing, etc., in this bulletin may be regarded as official. See also, *Journal of Infectious Diseases*, 1905, Supplement No. 1, p. 284–294.

following statement by Bosanquet represents the present status as to standard serum in this country also: "Unfortunately no standard strength is adopted in the serums on the market. The dose is generally calculated in cubic centimeters, without any statement of the number of units contained, so that not only is accurate dosage impossible, but cases recorded as treated with antitoxin have very little value owing to the impossibility of knowing how many units of antitoxin were really used."

Like antibodies in general, many antitoxins occur in normal animals. Diphtheria antitoxin occurs in small quantities in about 50 per cent. of human beings and in about 30 per cent. of horses. We know very little about antitoxins except from their specific actions. They are found in the fluids of the body, especially in the blood and milk. They are changed by heating to 60 to 70° C. and by exposure to light; when dried they tolerate higher degrees of heat and may be kept for a long time. It has been very difficult to free the antibodies from serum albumin and serum globulin. By fractional salting out of proteins Pick found that euglobin or pseudoglobulin contains all the antitoxin, the kind of globulin concerned depending on the kind of animal and the kind of toxin used for immunization. The question whether toxins, antitoxins, and other bodies concerned in the reactions of immunity, are colloidal substances purely, is now being discussed. Pauli emphasizes the many similarities between the reactions of immune bodies and colloids, while Bechhold points out that the colloid nature of toxins, for instance, is yet to be established, at the same time as he was one of the first to call attention to the analogy between the precipitation of colloid suspensions and agglutination.

The Neutralization of Toxin by Antitoxin.—The early explanations of the action of antitoxins were largely vitalistic. The idea that antitoxin is a changed toxin fell to the ground because the amount of antitoxin produced is out of all proportion to the amount of toxin injected; and because of the reproduction of antitoxin after bleeding immunized animals. At the present time neutralization of toxin by antitoxin is regarded as the result of chemical union into harmless and fairly stable compounds. The study of the union of toxin and antitoxin was furthered by Ehrlich in selecting for this use toxins that act in vitro as well as in vivo. In this way the difficulties of the use of living animals were largely overcome. The effects of blood-laking toxins of bacterial origin (hæmolysins like tetanolysin, etc.) and their antitoxins, and of vegetable agglutinins for red corpuscles (ricin, abrin, crotin, robin) and their anti-agglutinins, as well as of certain ferments that give rise to antiferments, are easily followed in the test-tube. In experiments with hæmolysins and antihæmolysins, red corpuscles, freed from all serum, are used as indicators of the effects of various mixtures, the laking being measured by means of simple colorimetric scales. The results of these experiments show that toxic and antitoxic action may take place without the immediate coöperation of the living organism, and that the combination toxin-antitoxin follows chemical laws. The rapidity with which toxin and antitoxin unite depends on the degree of concentration, temperature, medium, amount of salts present, etc. In several instances it has been shown that they obey the laws of multiple proportions. The same general laws appear to govern the union of other antibodies with the substances upon which they act.

Toxins must be regarded as having a greater avidity for antitoxin (free-cell receptors) than for fixed cell receptors, or at least as great; were this not so it would be difficult to explain the action of antitoxin. Recent union between toxin and cells may be broken up by antitoxin. This is shown in Madsen's experiment of "healing in the test-tube," in which antitetanolysin was found to prevent laking of corpuscles by tetanolysin even after the latter had become united with the corpuscles. In this way may be explained the good effect of antitoxin in large doses after characteristic symptoms have developed. As time goes on, however, the union between toxin and cell becomes firmer and firmer, and the antitoxin soon loses the power to separate the toxin from the cell—*i.e.*, to arrest the toxic action. This shows the necessity of early administration of antitoxin in large doses in diseases like diphtheria and tetanus—lessons taught also by clinical experience.

Ehrlich demonstrated that there is no fixed relation between the toxicity of diphtheria toxin, as represented by the soluble products of diphtheria bacilli in broth cultures, and its power to combine chemically with diphtheria antitoxin. Various influences—time, heat, light, etc.—reduce its toxicity without altering its power to combine with antitoxin. Thus it became necessary to establish an arbitrary standard of antitoxin, which is more stable than toxin, by comparison with which other antitoxic serums might be standardized. An accurately tested serum was carefully dried for preservation and is now used as a standard. As the antitoxin unit or immunity unit, Ehrlich established that quantity of antitoxic serum that will neutralize 100 lethal doses (M L D.) for guinea-pigs weighing 250 grams. Two important limits (limes) are established, namely, (1) L°, by which is meant the amount of toxin that exactly neutralizes one immunity unit of antitoxin, and (2) L+, by which is meant the amount of toxin that will neutralize one unit of antitoxin + the amount necessary to kill a guinea-pig, weighing 250 grams, in 4 days. Ehrlich now showed that, when the L° quantity of toxin is partially neutralized by adding fractional amounts of antitoxin, there is at first no decrease of toxicity in the mixtures, as there should be if the true toxin were bound by antitoxin. Evidently the crude diphtheria poison contains certain substances that are non-toxic at the same time as they bind the antitoxin with greater avidity than the toxin proper. The body which has the greatest affinity for antitoxin is called by Ehrlich *prototoxoid*. It may require as much as one-fourth of the immunity unit to saturate the prototoxoids in the L° dose of poison. From now on the toxin diminishes in toxicity in exact proportion to the amount of antitoxin added. When, say, two additional fourths of the antitoxic unit have been added to L° of toxin, the mixtures no longer produce acute death, but local œdema and late paralysis, and this is accounted for by Ehrlich as due to another toxic body with less affinity for antitoxin than toxin and prototoxoid, and designated as *toxone*. The difference between toxoid and prototoxoid is this, that the latter has a stronger avidity for antitoxin, while toxoid in this respect equals toxin proper. Both toxoid and prototoxoid are without active toxophore groups. Ehrlich's explanation of the fact that a certain amount of antitoxin may be added to the crude diphtheria poison without lessening its toxicity has been accepted generally. His belief, however, that the poison contains two active toxins—namely, the diphtheria toxin proper and toxone—has been attacked by Arrhenius and Madsen, who have given these phenomena a simpler interpretation in that they regard the reactions between

toxin and antitoxin as reversible, analogous to the reactions between other substances of feeble affiinty, and consequently obeying the Guldberg-Waage law of mass action. They have calculated the constant K for a number of combinations. It has been pointed out, however, that the mixtures are not homogeneous, and that the degree of reversibility, if any really exists, is extremely small; and at present the Ehrlich interpretation of toxin and toxone seems to have the greater number of followers.

Lysins (Bacteriolytic and Hæmolytic Amboceptors).—Bacteriolysis, or the solution of bacteria by normal and immune serum, is a complex process. Nuttall first brought definite proof that defibrinated blood and other fluids are bactericidal. Buchner regarded the bactericidal substances of blood as the principal protective agents against infection, and for this reason he named them alexins (αλεξειν = to guard). Later investigations have shown that there is no concordance between natural immunity and the bactericidal power of the serum as now understood. Thus human serum is strongly bactericidal to typhoid bacilli, and yet as typhoid fever establishes itself there develops a typhoid bacillæmia. On the other hand, dog serum is not harmful to anthrax bacilli, and nevertheless the dog is naturally immune to anthrax.

R. Pfeiffer first observed that cholera germs placed in the peritoneal cavity of a guinea-pig, immunized to cholera, undergo lysis—"Pfeiffer's phenomenon." Before long similar phenomena were observed with respect to typhoid, pest, and other bacteria. Pfeiffer showed, further, that lysis occurs also when cholera germs are placed in the body of a normal guinea-pig provided they are mixed with the serum of an immune animal. As the unit of immune cholera serum, Pfeiffer designates that amount that saves a guinea-pig weighing 200 grams from 10 times the fatal dose of an eighteen to twenty-four hour old agar culture of cholera bacteria mixed with the serum, the total quantity of the mixture always being 1 cc. Pfeiffer's antibodies, as the active substances in the immune serum were called, were found to be strictly specific. Pfeiffer first believed that his antibodies could be activated only by something in the body of living animals; but Metchnikoff and Bordet demonstrated that the destruction takes place in vitro also, when normal serum is added to immune serum.

The study of bacteriolysis received great benefit from the discovery by Bordet[1] that repeated injections of an animal with the red corpuscles of another species gives rise in the blood of immunized animals to a specific substance that *in vitro* lakes the red corpuscles injected, in the same way as immune bacteriolytic serum causes lysis of corresponding bacteria. This was studied thoroughly by Ehrlich and his coworkers, and to them we owe theoretical explanations that have proved most helpful. Strictly speaking, laking of red corpuscles should not be called lysis, because in most cases the corpuscles are not really dissolved. With this restriction hæmolysis and bacteriolysis follow the same scheme. The serum of normal animals and of man contains several hæmolytic and bacteriolytic bodies, and by immunization with animal and bacterial cells, as well as cellular disintegration products, the amount of lysin may be increased in a specific manner, or entirely new lytic substances may be produced. Nissen, v. Behring, and

[1] The same discovery was made by Landsteiner and by von Dungern quite independently.

Bouchard, were the first to show that immunization with certain bacteria greatly increases the bactericidal power of the serum.

The attached or free-cell receptors that give rise to lysins have been called lysogens. Intravenous injections of cholera germs require only minute quantities to produce immunity. Pfeiffer and Friedberger have determined that 0.004 mg. of bacterial substance containing 0.000,000,4 gm. of active bacterioprotein gives rise to amboceptors enough to cause the solution of 300,000,000 times the amount of bacteria injected. Conradi, Neisser and Shiga, Strong, and others, have demonstrated that autolysis of typhoid, dysentery, and cholera bacteria killed by heat sets free bacterial receptors—lysogens—which on injection in sterile filtrates give rise to immune bodies—*i.e.*, to active immunity. Wassermann recommends for artificial immunization against typhoid fever and cholera, powder obtained by evaporation in vacuum of the fluid that results when suspensions of bacteria are killed by heat and allowed to digest themselves (autolysis).

Baumgarten, Fischer, and others, have urged that the bactericidal action of normal and immune serum is due to purely physical factors, especially osmotic disturbances, and lack of assimilable food substances. But this view has had to give way in favor of more specific action. Nor has it been possible to explain bacteriolysis as due to alkalinity, which, however, may play some role in the process. Landsteiner and Eisler suggest that lysins act through some kind of union with the lipoid and protein substances in the membranes of cells and bacteria. They found that ethereal extracts of animal and bacterial cells bind various lysins.

Both normal and immune lytic sera cause lysis by virtue of two distinct interacting substances, one as a rule destroyed by heating at 55° C. for 30 minutes, the complement, and one that is more thermostable (Bordet). Serum that has lost its lytic power on account of destruction of the complement by heat or otherwise is said to be inactivated; it may be reactivated by the addition of fresh serum containing the suitable complement only. The thermostable body, commonly called immune body or amboceptor, is the one that is produced in a specific manner during immunization as the result of an overproduction of cell receptors. Amboceptors are assumed by Ehrlich's theory to be free cell receptors, which differ from antitoxins in having two haptophore groups, one by which they unite with the receptors of the corresponding bacterial or other cells—the cytophile group—and one by which they unite with the thermolabile complement—the complementophile group. In itself the amboceptor is without any destructive action.

The importance of cell receptors in causing the formation of amboceptors is shown very clearly by an experiment of von Dungern's. He found that blood corpuscles loaded with amboceptors from digestion in heated immune hæmolytic serum no longer were able to start the formation of amboceptors when injected into the proper animal. The receptors of the corpuscles being occupied, they could not unite with receptors in the cells of the animal injected, hence there was no setting free of new receptors (amboceptors).

Amboceptors are fairly stable bodies; heating to 60° C. for twenty hours has no marked effect upon them, but heating to 70° C. for one hour destroys them. They are non-dialyzable and may be kept for years. Manwaring has shown that in serum heated sufficiently to destroy the complement only, it is possible to demonstrate the presence of substances that on the one hand favor and on the other hand inhibit hæmolysis. These substances prevent

the determination of the physicochemical laws of the union of amboceptors with corpuscles.

Not all bacteriolytic serums are thermolabile. Alice Hamilton has found that rabbits and goats immunized to virulent pseudodiphtheria bacilli contain specific bacteriolytic substances that are rendered inactive only by heating at 88° C. for one hour. Jessie Horton finds that the anthracidal action of normal white-rat serum, ascribed by Behring, Pirenne, and others to its alkalinity, is more likely due to a thermostable anthracidal substance that makes its appearance as the animals grow older; soon after birth the serum is inactivated by heating at 56° C. for thirty minutes. The exact nature of these substances, whether simple or complex, has not been determined. They may well be simple bacteriolytic substances with two groups, namely haptophore and toxophore. Woelfel and Levaditi have described thermostable hæmolysins in normal serum.

The same serum may contain several amboceptors, and the amboceptors in different serums differ as a rule. Amboceptors capable of uniting with the same cell, bacterial or otherwise, may differ in two respects; namely, in their cytophile and in their complementophile groups. The same amboceptor may be able to unite with several complements by virtue of possessing several complementophile groups (polyceptor). A serum may contain amboceptors for a certain cell but not any suitable complement, as in the case of dog blood, for instance, which contains an amboceptor readily taken up by anthrax bacilli; the complement necessary to complete the lysis may be found, however, in some other animal, *e. g.*, the rabbit. The researches of Flexner and Noguchi have shown that cobra and other venoms play the part of amboceptors in hæmolysis, and Kyes showed that lecithin may act as complement to the venom amboceptors.

The complements are sensitive, ferment-like substances normally present in blood; and are not increased by immunization with foreign cells. Blood contains many kinds of complements, and not merely a single one, as usually claimed by French investigators; and the complements in different bloods may differ as to the affinities of their haptophore groups. Complements in general are neutralized by various salts in dilute solutions ($CaCl_2$, $BaCl_2$, $SrCl_2$, $KFeCN_6$, $Na_2C_2O_4$, $Na_3C_6H_5O_7$, etc.), so that there is a close relationship in their physicochemical properties. Now when complement is attached to a red corpuscle or a bacterial cell by means of the amboceptor, it causes lysis (bacteriolysis, cytolysis) by virtue of the action of its zymotic group. Complements, then, resemble toxins in that they have two atomic groups, haptophore and toxophore or zymotic. The toxophore group may be rendered inactive, while the haptophore group retains the power to unite with the amboceptor; the complement is now said to have changed into complementoid.

Antiamboceptors occur normally. Pfeiffer and Friedberger describe a body with antibacteriolytic action in normal serum containing amboceptors for typhoid and cholera germs. Whether antiamboceptors capable of occupying the cytophile groups of the hæmolytic amboceptors may be produced artifically appears to be questionable. Antiamboceptors with haptophore groups similar to those of complements, and consequently the equivalent of complementoids, are described by Bordet and Ehrlich and Sachs. Free bacterial receptors might act as antiamboceptors by occupying the cytophile groups of amboceptors.

The brief duration of immunity, especially the antitoxic as well as the anti-infectious, has given rise to considerable speculation, especially as the specific substances, such as antitoxin, disappear rapidly from the blood and in some other way than in the secretions. V Behring made the interesting observation that in horses the passive immunity to tetanus lasts much longer when it is due to the injection of homologous antitoxic serum than of heterogenous. This led to the suggestion that possibly the injection of heterogenous serum gives rise to precipitins and precipitates that carry with them the specific antibodies. Dehne and Hamburger observed that the addition of a precipitating serum (precipitin) to antitoxic horse serum made the latter inactive. This has been confirmed by Sacharoff, and Kraus and Pribram. As regards bacteriolytic serum Pfeiffer and Friedberger believe that the amboceptors in immune serum (antibacterial) may give rise to antiamboceptors, because they found that the immunity produced by cholera bacteria laden with amboceptors by treatment with immune serum and then washed, is not any longer in duration than that from injections of serum alone. In this way they believed that they could exclude the possibility of specific precipitation. Wassermann and Bruck reach the same conclusion. In their experiments they first removed all precipitable substances without any loss of amboceptors, but without being able thereby to prolong the passive immunity.

Under certain circumstances, when amboceptors are present in excess, it has been conceived that the complementophile groups of free amboceptors may unite with complement to such an extent that lysis is markedly diminished, if not suspended entirely, because of the lack of complement for the amboceptors that have become attached to the cells. This is known as deviation of complement (Neisser and Wechsberg). According to Bordet's theory the amboceptor modifies the cells in some way, so that they are rendered susceptible to the action of the complement, which he thinks does not unite with the amboceptor. Now deviation of the complement by free amboceptor does not harmonize with Bordet's conception of the mode of action of the amboceptor. Complement deviation may be of practical importance, as possibly the satisfactory action of a bacteriolytic serum depends on a certain balanced relation between complement and amboceptor. Anticomplements, normal as well as immune, have been described by various investigators, but there is some doubt as to the conclusiveness of the experiments because Gengou, Moreschi, and Gay "have shown that in immunization with serum, antibodies directed against the albuminous constituents are formed which, by uniting with the corresponding albuminous bodies possess the power of exerting anticomplementary action." Here dissolved albuminous bodies and not complements are the antigens. This neutralization of complement by serum + antiserum—antigen + antibody—is now being used for the purpose of demonstrating the presence of infectious materials and immune bodies in the fluids and tissues of patients with various diseases (Wassermann).

Opsonins (Phagocytosis).—The discovery by Wright and Douglas of the presence in normal blood of certain substances called by them opsonins,[1] which render various bacteria susceptible to phagocytosis, has stimulated anew the interest in this process. It has been shown conclusively

[1] From the Latin *obsono* or *opsono*, "I cater for," "I prepare food for."

that phagocytosis of many bacteria by the leukocytes is wholly dependent on these special substances, which become attached to the bacteria and in some as yet unknown manner so change them that they are readily taken up by polymorphonuclear leukocytes. Leukocytes freed from serum by washing do not take up bacteria suspended in salt solution. Bacteria treated with opsonic serum and then freed from serum by washing are taken up by washed leukocytes. Bacteria so treated may be designated as sensitized, but sensitized or opsonified bacteria are not necessarily altered recognizably in form or function, and many bacteria multiply freely in sera that contain opsonin. Normal opsonins are largely destroyed by heating at 60° C. for thirty minutes, some being more resistant than others. At 0° C. normal opsonins may be preserved for several days; at 36° C. they deteriorate quickly. Like complements, they are neutralized or bound by various salt solutions and other substances such as formalin and lactic acid so that they cannot act on bacteria. Opsonins may be conceived as having a structure like that of agglutinins, toxins, complements, precipitins, and to possess at least two groups, a haptophore, by which they attach themselves to bacterial and other cells, and a functional, by which is produced the change in the cell that makes it phagocytable.

There is abundant evidence that immunization with suitable bacteria and red corpuscles may give rise to immune opsonins. Wright and Douglas noted a marked increase in the opsonic power of the serum of patients suffering with chronic staphylococcus infections, after injections of 0.75 to 1 cc. of heated broth cultures of staphylococci. They also showed that the opsonic power with respect to tubercle bacilli greatly increases in response to inoculations of tuberculin. On the strength of these and other facts Wright has developed his method of treatment of infections with vaccines of the infecting bacteria, the opsonic index being used as a guide for the injections. Several years ago Denys and his coworkers observed that rabbit leukocytes in normal serum ingested the avirulent strain of a streptococcus, but not the strain made virulent by repeated passage through animals. In the serum of immunized rabbits and horses, however, the leukocytes were found to have marked phagocytic power over virulent streptococci. Bordet, Besredka, and v. Lingelsheim, all noted the greatly increased phagocytosis of streptococci in the presence of immune serum both in vivo and in vitro, and the Belgian and French investigators ascribed the cause to stimulation of the phagocytes.[1] Recently Neufeld and Rimpau showed that leukocytes, digested in antistreptococcus serum and then suspended in normal serum, do not take up virulent streptococci. But digestion of virulent streptococci with antistreptococcus serum, then washing them in NaCl solution and mixing them with leukocytes, resulted in marked phagocytosis. They made analogous observations with reference to pneumococci, thus showing conclusively that the immune serum may so change certain virulent bacteria that leukocytes ingest them. It has been shown too, that in many infections there is increase of opsonin for the corresponding bacterium at some stage of the disease, *e.g.* at the time of crisis in pneumonia (Wolf).

Savtchenko and others, and recently Neufeld and Töpfer, Barratt, and

[1] Metchnikoff has designated substances that have been assumed to stimulate phagocytes as "stimulins." Whether there are real stimulins has not been determined. It seems probable that much of what has been regarded as stimulation in reality is the result of opsonification.

Hektoen have shown that the serum of animals immunized with alien blood commonly contains opsonin for the corpuscles in question. Human serum may contain opsonin for human erythrocytes (iso- and auto-opsonin).

Neufeld and his coworkers propose to call the substances that render bacteria and corpuscles susceptible to phagocytosis, bacteriotropic and hæmotropic substances. As already pointed out, Wright and Douglas in 1903 suggested that substances of this kind should be called opsonins, and in view of the priority of their suggestion, as well as the appropriateness and adaptability of the term opsonin, it would be well to apply it also to the opsonic substances that arise in consequence of immunization either with bacteria or animal cells. We may speak of normal and immune opsonins for bacteria and for red corpuscles (bacteri-opsonins and hæmopsonins). There is every reason to believe that opsonins are distinct from and that they are specific in the same degree as other antibodies.

The demonstration that opsonins render various bacteria susceptible to phagocytosis does not prove fully that these substances are of any importance in infections. It must be shown that phagocytosis is essential for the destruction of certain bacteria by the blood. Denys showed that in mixtures of normal rabbit leukocytes and normal rabbit serum there was little or no destruction of virulent streptococci, whereas, when immune serum was substituted, prompt phagocytosis with complete destruction of the streptococci took place.

The serum of normal persons and of patients with streptococcus infections has no streptococcidal effects, but constitutes a good medium for streptococci. Ruediger has shown that normal defibrinated human blood has some streptococcidal effect; that blood from patients with acute infections and leukocytosis has much greater destructive effect; and that the higher the leukocyte count the greater this effect. He shows, too, that the opsonin in the serum must be present in the mixtures in order that streptococci may be destroyed. Rosenow has made analogous observations with respect to pneumococci.

It is extremely probable that the relative immunity of the dog to anthrax is due to phagocytosis. Virulent anthrax bacilli grow freely in normal dog serum and in suspensions of washed dog blood corpuscles, but are destroyed in defibrinated dog blood, and this is associated with marked phagocytosis. Destruction also takes place when normal serum is added to washed corpuscles and when bacilli, sensitized in normal serum, then washed, are mixed with washed corpuscles or leukocytic exudate. The essential role of intraleukocytic destruction of the bacilli is shown also in plates made with decreasing quantities of blood and a fixed quantity of bacilli, the total quantity being kept at 1 cc. in all cases by adding normal dog serum. The destruction decreases as the corpuscles (leukocytes) decrease.

The prompt and pronounced phagocytosis of different bacteria in the peritoneal cavity in the presence of specific immune serum indicates that opsonins play the same part in vivo as in vitro, and we have in opsonins a new form of antibody that must be reckoned with, especially in the explanation of immunity to and healing of those infections that are caused by bacteria, the destruction of which is not accomplished by free lysins (streptococci, pneumococci, etc.).

Precipitins.—In 1897 Rudolf Kraus of Vienna discovered that the serum of an immunized animal forms precipitates with substances in the sterile

filtrates of broth cultures of the corresponding bacterium. This reaction was found to be quite specific but in certain cases no precipitate is formed (B. diphtheriæ). In 1899 Tschistowitsch and Bordet found that serum of an animal injected with alien serum causes precipitates in the alien serum. Fisch observed that injection of epithelial cells gives a serum that precipitates the casein in milk. We may speak of bacterioprecipitins, zoöprecipitins, and phytoprecipitins. Wassermann and Schütze, and Uhlenhuth applied the reaction to the differential diagnosis of human and animal blood and albumins, and the precipitation method or test is now established firmly in forensic medicine. Nuttall[1] has made extensive studies into the biological relationship of animals by means of precipitating sera, and he has devised a method of volumetric measurement of the precipitate in order to determine the relative values of the reactions obtained.

Kraus and others have found precipitins for alien serum in the organs and blood of normal animals; but the normal occurrence of bacterioprecipitins has not been observed definitely. The presence of precipitable substance (precipitinogen) is demonstrated by means of specific immune serum. In man and animals precipitinogen is present in the blood, the organs, in milk, and in various pathological products (inflammatory exudates, transudates, albuminous urine, etc.). Precipitinogen of bacterial origin may be secured by means of filtered extracts with NaCl solution of agar cultures and in filtrates of broth cultures. Numerous efforts have been made to obtain this substance in pure form, but as yet the results are somewhat conflicting.

It is generally agreed that precipitinogen is part of a protein molecule that possesses considerable resistance to high temperature, alcohol and ether, decomposition, and various digestive ferments. Precipitin is not formed by all animals. Animals do not form precipitins active against their own sera, and closely related animals do not produce liberal quantities of precipitin when injected with the serum of one another. In suitable animals precipitin appears in the blood in from four and one-half to five and one-half days after injection of precipitinogen. Obermeier and Pick found .02 gram of albumin and Schur .004 gram, enough to cause demonstrable precipitin. To obtain specific precipitin for the forensic testing of suspected human blood it is customary to immunize rabbits for weeks with human serum.

Kraus and Pirquet as well as others have shown that precipitin is a complex body composed of two atomical groups, a more stable haptophore group by which it unites with precipitinogen, and a more labile functional group by virtue of which precipitation takes place. This functional group is destroyed by heating at 58 to 60° C. in the case of bacterioprecipitin, and at 70° C. in case of milk precipitin (Müller) and albumin precipitin (Eisenberg). Precipitoid also develops as precipitin stands outside of the body. In a mixture of precipitin and precipitoid the latter may have the greater affinity for precipitinogen in concentrated serum; therefore precipitoid might bind all available precipitinogen. When dry, precipitin may be heated to 100° C. for a half hour without damage; it is destroyed at 130° to 135° C. Kraus and Eisenberg have demonstrated the development of antimilk-precipitin and Schütz of antiserumprecipitin.

When precipitin and precipitinogen are mixed, a precipitate develops. The precipitation is more rapid in case of animal precipitin and serum than

[1] *Blood Immunity and Blood Relationship*, Cambridge, 1903.

in case of bacterial filtrates and bacterioprecipitin. In the latter instance the reaction becomes apparent usually after a few hours, first as a cloudiness, then flocculi appear which settle to the bottom as amorphous masses, leaving a clear supernatant fluid. The reaction is furthered by a temperature of 37° C. and acid reaction (Rostoski). Neisser and Friedberger have observed that the precipitation that occurs when eosin and bismarck brown are mixed—colloids of opposite electrical charge—presents certain analogies with serum precipitation. Serum precipitate contains albuminous bodies but is insoluble in mineral salts, in sodic hydrate, and resists digestion. Whether precipitation occurs in the body or not seems to be doubtful, and further investigations are necessary on this point. Recently it has been suggested that the evil effects observed after the injection of various therapeutic sera of animal origin are due at least in part to the formation of specific precipitins and actual precipitates in the body but von Pirquet and Schiek have shown that there is no relation between the formation of precipitins and the appearance of the serum disease.

As stated, bacterioprecipitins are quite specific. In the case of colon bacilli, immunization with one strain results in precipitins for related strains, but to a much less extent than for the homologous strain. Norris found that sera of rabbits immunized to four species of the colon-typhoid group precipitated filtrates of all the species of the colon-typhoid group tested, but more quickly and more copiously in case of the homologous filtrates, and in high dilutions only in the latter. It is assumed that the filtrates contain diverse precipitinogens which on immunization give rise to numerous partial percipitins. Serum precipitins are also specific, but on account of the variety of precipitinogens in a given serum the immune serum may contain a corresponding variety of precipitins, the specificness of which, however, is demonstrable by means of selective absorption (Ascoli) and by increasing dilutions.

Agglutinins and Agglutination.—Gruber and Durham, while studying Pfeiffer's phenomenon, were the first to observe tha agglutination is a specific reaction. The reaction of agglutination was applied almost at once as an aid to the diagnosis of typhoid fever by Grünbaum and by Widal. Its use has extended to other infectious diseases as well as to the tentative identification of bacteria suspected of causing infectious processes. Other objects besides bacteria are subject to agglutination; *e. g.*, red blood corpuscles may be agglutinated not only by normal and immune[1] alien sera, but also by toxic substances of animal, plant, and bacterial origin. Certain bacteria also produce hæmagglutinins, and it is believed that certain thrombi observed in infectious diseases owe their origin to agglutinins derived from bacteria. Human serum, however, contains agglutinins for the corpuscles of other individuals (iso-agglutinins) and it may be that at times auto-agglutinins develop.

Normal sera in general contain small quantities of various kinds of bacterio-agglutinins also, especially for the bacteria of typhoid fever, cholera, and dysentery, as well as for colon and pyocyaneus bacilli. When a normal human serum has a relatively high agglutinating power against a given bacterium the possibility of a previous infection must be considered. Immune as distinguished from normal agglutinins develop either in spon-

[1] By immune in this case is meant the serum of an animal injected or immunized with the corpuscles of another species..

taneous infections or as the result of artificial immunization by various procedures. J. McCrae found that the substances that induce agglutinins to form—the agglutinogens—pass through the walls of collodion sacs filled with bacterial cultures and placed within the abdominal cavity of rabbits. The power to cause agglutinins to form in the animal body is possessed by bacteria in general, but some have this power in higher degree than others. The agglutinability also varies; the typhoid bacillus when first isolated, for instance, is sometimes quite inagglutinable. It follows that the agglutinogenic power may vary also.

The bacterial receptors that by their union with cell receptors give rise to agglutinins are called agglutinogens. When attached to the bacteria they constitute the agglutinable substance so-called; *i. e.*, by uniting with them the agglutinins are able to cause the change in the bacterial cell by virtue of which clumping takes place. There is evidence that the same bacterium may possess different agglutinogens and consequently give rise to different agglutinins when injected into proper animals. Theobald Smith and Reagh have shown that motile bacilli may give rise to agglutinins that act upon the flagella, and others that act upon the bodies of the bacteria (flagellar and somatic agglutinins). Beyer and Reagh found the flagellar and somatic agglutinins and agglutinable substances of the hog-cholera bacillus may be differentiated by heat. Park and Collins have studied especially the production of specific and non-specific agglutinins by the same bacteria.

Agglutinins, theoretically, are free animal-cell receptors analogous in structure to toxins; *i.e.*, provided with two atomic groups, one haptophore, whereby they unite with agglutinogens, and one zymophore, that causes the alteration in the bacterial cell upon which agglutination depends. By heating for some time between 60 and 80° C., by exposure to acids and alkalis, and by long standing, the zymophore group is lost and the agglutinin is transformed into agglutinoid. Agglutinoid has the power to unite with agglutinogen and by so doing it can prevent agglutination by the subsequently added intact agglutinins. Fresh serum may contain agglutinoids with stronger affinity for agglutinogen than agglutinin, and hence called pro-agglutinoids. In such cases the presence of agglutinin may be revealed by diluting the serum highly so that the pro-agglutinoids no longer can influence the reaction. Agglutinins withstand digestion with pepsin and papayotin, but not prolonged tryptic digestion. When serum is dried and carefully preserved agglutinins remain intact for months and years. In immunized animals agglutinins occur in greatest quantity in the blood, and this has led to the suggestion that they are produced by the leukocytes; they are present also in various body fluids, especially milk, and in organ extracts. The power in different animals to form agglutinins varies, and the amount of agglutinin in the blood of the same patient or animal may alter considerably from day to day.

A good deal of work has been devoted to the relations between agglutination and bacteriolysis, which at one time were thought to be due to the same substances; but the idea that the specific agglutinins and bacteriolysins in immune serum are identical has lost all support—even that of its originator (Gruber). It has been found (1) that the serum of cholera and typhoid convalescents may be strongly bactericidal, while the agglutinating power is no more marked than in normal serum (Pfeiffer and Kolle, Bordet); (2) that in certain cases immunized animals give only agglutinins and not

bacteriolysins; (3) that immune serums may lose their bacteriolytic power but retain their agglutinating property, and *vice versa;* (4) that in immunization the curves of agglutinating and bacteriolytic substances as they appear in the blood are by no means parallel (Park and Collins, Deutsch); (5) that the agglutinogens and lysogens in bacterial bodies may be different and separable by various means—*e. g.*, different resistance to high temperatures (Defalle), precipitation (Wassermann).

As agglutination takes place the corresponding agglutinin is removed from the serum; free agglutinogens also bind agglutinin in a specific manner. It is consequently possible by means of selective absorption experiments to demonstrate the presence of more than one agglutinin in the same serum.

Immune serum may agglutinate organisms that are closely related to the homologous[1] bacterium. The typhoid-colon group furnish many examples of this "group agglutination," in which case it concerns the actual new formation of agglutinins for the related or heterologous organisms. It is generally stated that the agglutinin for the homologous organisms is always present in the largest quantity, and it is therefore spoken of as the chief agglutinin; while the weaker agglutinins for the heterologous organisms are called partial or adventitious or common agglutinins. Park and Collins have shown, however, that if immunization is continued for a long time the relative amounts of specific and non-specific or common agglutinins may vary from time to time, and that the common agglutinins may equal or exceed the specific in amount. Undoubtedly many conflicting statements in regard to the agglutinability of closely related bacterial species are due to the belief that the specific always exceed common agglutinins in relative strength. Durham offers the following explanation of group agglutination which shows that this phenomenon does not necessarily go contrary to the specificness of agglutination by immune serum: "The typhoid bacillus contains certain constituents, agglutinogenic molecules, which one may designate as a, b, c, d, and e; these differ among themselves in unknown respects, but each is able to stimulate the formation of a corresponding agglutinin. The serum, then, would have the agglutinin molecules A, B, C, D, and E, also differing among themselves, but having at least one property in common—that of causing agglutination of the typhoid bacillus by uniting with their corresponding agglutinogenic molecules. In this sense nothing could be more specific. Bacillus enteriditis, closely related to the typhoid organism, may possess the agglutinogenic molecules c, d, e, f, g, and h, and following the principle expressed above would stimulate, in the body, to the formation of agglutinin molecules, C, D, E, F, G, and H. Inasmuch as the agglutinogens c, d, e, are common to the two bacilli, the agglutinins C, D, and E would effect either of the two organisms. The typhoid serum would contain five agglutinins for the typhoid serum and only three for Bacillus enteriditis, consequently the action would be stronger against the typhoid bacillus." It is a general rule that the agglutinins, specific as well as common, set free by one bacterial species, may be removed from the serum by adding sufficient quantities of that species. Other bacteria would remove those common agglutinins for which they present the proper affinity.

At first, agglutination was regarded as the result of an abnormal viscidity of the bacteria (Gruber and others) or as due to the formation of a sticky

[1] By homologous is meant the bacterium used for immunization of the animals furnishing the serum.

precipitate upon them (Paltauf), but lately, Bordet's conception of agglutination as similar in nature to the precipitation of colloid suspensions has received strong support, especially from the work of Bechhold, Neisser and Friedemann, and Landsteiner.[1] Agglutination occurs after agglutinin has combined with the bacteria[2] (forming the so-called agglutinin-bacteria) which becomes clumped and settle down, provided salt is present (Joos). It is believed that the same laws govern agglutination of bacteria as govern precipitation of colloids and other particles (kaolin, mastic) in suspension. Like colloid and other particles, bacteria behave like negatively charged particles in electrical currents in that they migrate to the positive pole. Now the power of a salt to precipitate colloids or agglutinate bacteria has been shown to depend (1) on the degree of its electrolytic dissociation; (2) on the valency of its cation; (3) on the speed of migration of the cation; and (4) its decomposition tension. "The higher the valency of the cation and the lower its decomposition tension the greater, in general, is its power to precipitate colloids and bacterial suspensions. H-ions form a striking exception to this rule, presumably on account of their high speed of migration. Sodium, for instance, has a high decomposition tension, and its valency is low, and in agreement with this it has been found that its salt, NaCl, precipitates colloids only when used in high concentrations, and does not agglutinate bacteria at all, unless they have previously been acted upon by agglutinin. That is, agglutinin-bacteria are more susceptible to the action of NaCl than untreated bacteria. On the other hand, salts of metals with a high valency and a low decomposition tension, as $Al_2(SO_4)_3$, precipitate untreated bacteria when only small quantities of salt are added." The cation, being positively charged, attracts bacteria or other particles and neutralizes their electrical charges with the formation of clumps that fall out of suspension (Billitzer). Now the role of agglutinin appears to be to reduce the amount of negative electricity the bacteria carry and thus to render the bacteria more susceptible to the clumping action of the salts present in the fluids. All salts clump agglutinin-bacteria more readily than they do normal bacteria. The mechanism of specific precipitation is regarded as identical, only the particles are smaller. Agglutination and precipitation depend, then, upon the action of salts upon the electrical charges that keep the particles suspended.

[1] Landsteiner and v. Esler. *Centralbl.* f. Bakt. 1, Abt., Orig., 1905, XXXIX, 309.

[2] The various conceptions concerning this union are discussed by Craw, *Journal of Hygiene*, 1905, v, 113.

CHAPTER II.

TYPHOID FEVER.

By THOMAS McCRAE, M. D.

"Typhoid fever is a Protean disease, whether considered in its clinical, its pathological or its bacteriological aspects."—FLEXNER.

Introduction.—Typhoid fever is a general infection with the bacillus typhosus characterized especially by involvement of the lymphoid tissues, usually by hyperplasia and ulceration of Peyer's patches, enlargement of the spleen and parenchymatous changes in certain other organs. There is no uniformity in the name given to it in various languages. While there may be objections to the name "typhoid," yet this is so firmly established that usage has sanctioned it and there is no confusion from it. As has been pointed out, we designate the causal organism as the *Bacillus typhosus*. In Great Britain the term "enteric fever" is in common use.

There is no disease with a more interesting history. Long confused with typhus fever, the distinction brought about slowly, it stands as an example of the difficulties which may attend the recognition of a disease. The views as to its nature have gradually changed. For a time regarded especially as a disease of the intestines, later we learned that it was primarily a general infection with secondary intestinal lesions. Then it was found that in some instances there was an absence of intestinal lesions, and that other organisms than the *B. typhosus*, although closely related, caused similar lesions. Local infections were proved to be possible without a general infection. In some instances the disease occurred as a terminal infection without any intestinal lesions.

In the explanation of the symptoms we have gone through different stages. Before the causal organism was discovered, the features of the disease were supposed to be principally due to changes occurring in the body of the patient. After the discovery of the causal bacillus, the specific infection and its results were held to be the most important, but as Ewing has pointed out, we may have given too little attention of late to the body itself. As he has emphasized, while the action of the bacillus and its products are important, yet much may be due to changes in the tissue cells of the body. After these have been injured or killed by the specific organism they will give rise to certain derivatives which are injurious in themselves and also appear to have an accumulative action. An analogy is suggested in some forms of acute yellow atrophy of the liver and also possibly in some of the cases of severe toxæmia in pregnancy. There are also suggestive findings in regard to the metabolism in typhoid fever. In many instances there are two marked changes: (*a*) a great increase in the urea nitrogen of the urine and (*b*) an increase in the ammonia and amido-acid nitrogen. It has been found that in some cases these are comparable to conditions in diabetes, leu-

kæmia and grave jaundice. The lesions found in the liver also support this view, especially as in some instances alterations like those found in acute yellow atrophy have been described. These suggest that changes in the body cells may be responsible for many of the symptoms and this may apply especially to the patients who die late in the disease with severe toxæmia.

As regards the bacillus, its toxins, the question of immunity, the explanation of relapse and other problems, there is much to learn. The length of time during which bacilli may live in the body after recovery from the disease shows that recovery from the disease does not necessarily mean the destruction of all the bacilli in the body. As regards the bactericidal power of the blood there are many doubtful points, thus relapses occur when this is very high or we may find very severe infections without many bacilli being found in the circulating blood.

The stamping-out of typhoid fever is one of the great tasks before the profession of this country. A disease now more of rural communities than of cities, its control offers many difficulties. In 1900 there were 35,379 deaths from typhoid fever in the United States. From 1900 to 1904 in the registration areas of the United States the death-rate was 33.8 per 100,000 of population. This was only exceeded by the mortality in Italy, was more than double the rate in England, and about three times that of Germany. The story is such an old one that little attention is paid to it. We of the profession shrug our shoulders and wonder at the apathy of the civic authorities. Are we guiltless? Every patient with typhoid fever means infection from a previous one. If thorough disinfection was carried out in every case of typhoid fever this year, and the same next year, what a decrease there would be in the incidence of the disease. Disinfection is often in the hands of people who do not realize the importance of its being thorough and it is no easy task for the physician to see that it is carried out. Too often he does not realize his own responsibility and is thoroughly satisfied if he brings the patient well through the attack, heedless of the danger to the community.

We are utterly illogical in our attitude to typhoid fever. We consider an ounce of cure worth many pounds of prevention. Nature is "careful of the type, careless of the single life," but we reverse her methods. A community is exposed to infection year after year and little is done for the many, but for the individual with the disease, hospitals, physicians and nurses work day and night. Think of the labor expended on one hundred patients to save the ten who are kept from death by care. How much better to remove the necessity of it!

From the mere side of the cost to the community, typhoid fever is important. Estimates may vary as to the value of the 35,000 people who die in the United States every year from typhoid fever. To be added to this is the cost of the illness of the 350,000 patients who recovered. To do this with accuracy is difficult but it is evident that the money cost of the disease is enormous. It has been estimated that typhoid fever in the South African War was directly responsible for an outlay of four million pounds. It is possible that the cost may bring home the seriousness of the problem to certain minds more forcibly than any statement regarding the number of deaths.

While typhoid fever with its great variety of symptoms has perhaps the first place in clinical interest for us, yet it is to its prevention that we must

devote the greatest attention. Perhaps nothing would aid this so much as improvement in the administration of the health boards through the country. It should be possible whenever an outbreak of typhoid fever occurs to immediately have an efficient sanitary authority with proper equipment take charge of the situation. If a state would establish such a bureau, get a good man at the head of it and give him sufficient powers, the occurrence of typhoid fever in that state would rapidly diminish.

HISTORICAL.

"Of no other disease can we read as full a history from American sources alone."—OSLER.

There have been fevers associated with delirium from the days of antiquity but it is not possible to recognize in the writings of Hippocrates or Galen exact descriptions which enable us to distinguish the different diseases which they grouped together, although certain enthusiastic writers believe that we can. Typhus and typhoid fevers, the plague, and perhaps relapsing and malarial fevers were grouped together. The disease described as "hemitritæus" was probably typhoid fever in many instances. The decrease in the "plagues" which visited Rome after the introduction of a system of water-supply and drainage suggests that some of these epidemics may have been typhoid fever.

While there are descriptions at earlier times which may be of typhoid fever, the history of its recognition really dates from the seventeenth century. The greatest difficulty was in the separation of typhus from typhoid fever; the malarial fevers, plague and relapsing fever were differentiated at an earlier period. There are records of doubtful cases by Spigelius and Bartholin, but there seems no doubt of the identity of the disease described by Willis.[1] He gives an account of an epidemic in 1643 among the troops fighting in the Civil War. Both armies suffered and the Royalists carried the infection with them to Oxford. A most interesting and complete account is given of a house epidemic in which five members of one family were attacked, one after the other, during a period of four months. Two of the five died. Among the features he described were headache, nose bleed, delirium, an eruption like flea bites, diarrhœa, abdominal distension, intestinal hemorrhage, incontinence of urine and fæces, emaciation in prolonged attacks, the long course and the slow recovery without crisis or the gradual progress to a fatal issue. He also noted that the outlook was grave in fat patients. In the history of one patient he describes what was probably an instance of death from perforation,—"pains and torments cruelly infected his belly, that crying out and moaning night and day, he sent forth most heavy complaints, his hypochondria and abdomen were tumid like a tympany and mightily distended." He made the observation that the contagion of this disease was slow but that gradually a household or a community might be infected, and mentions that some of those nursing the patients contracted the disease after a time. He appears to have clearly separated typhoid fever from the plague and typhus fever and appreciated

[1] Willis, *De Febribus*, Chap. XIV, "De Febribus Pestilentibus, ac Malignis in Specie, Aliisque Epidemicis"; and Chap. XVII, "De Febribus Epidemicis."

in a remarkable way many of the clinical manifestations and the features of epidemics. It seems that to Willis belongs the credit of the first accurate separation of the disease on clinical grounds. Sydenham describes a disease which was probably typhoid fever but makes no mention of an autopsy. Baglivi wrote of it under the name of "Febris mesenterica," a name given on account of the lesions in the intestine and the swelling in the mesenteric glands. Lancisi noted perforation of the bowel in some cases, while Hoffman in an epidemic in Halle in 1699 and again in 1728 apparently separated it from typhus fever, noted some of the clinical features and the ulceration of the bowel in fatal cases. He gave it the name of "Febris petechizans vel spuria." Panarolis in Italy described a disease which was evidently typhoid fever.

In the eighteenth century there were numerous observers who noted many of the essential features of typhoid fever. In the first half of the century Strother in England and Gilchrist in Scotland described a disease characterized by ulceration of the bowel and enlargement of the spleen which they termed "slow or slow nervous fever." Huxham of Plymouth in 1737 drew a sharp distinction between the slow nervous fever (typhoid) and the putrid malignant petechial fever (typhus). Manningham in England held much the same views as Huxham and separated the disease under the term of "Febricula." In England about the middle of the century there seems to have been a common recognition of this type of "intestinal fever," but whether it was definitely separated from typhus fever is doubtful and it was probably regarded as only a variety of the continued fevers. If the profession in Great Britain had paid less attention to the writings of antiquity and more to those of Willis, the matter might have been decided much earlier than it was, but it is evident that clinical observations without postmortem examinations could not do this or certainly did not. In Germany in 1748, Riedel described the disease under the title of "Darmfieber." Roderer and Wagler studied an epidemic in Göttingen from 1757 to 1762, which they discussed under the title "de morbo mucoso," and from their autopsy descriptions there can be no doubt that this was typhoid fever. The accounts of epidemics in Italy during the latter half of this century are without doubt of this disease. Morgagni described a case in considerable detail, noting the ulceration and perforation of the intestine as well as the swelling of the mesenteric glands and spleen. The principal fact established during this century was that a certain group of the cases with continued fever was characterized by intestinal lesions, but while the nature of these anatomical lesions was recognized there was no clear distinction between typhus and typhoid fevers, although the two types of "slow nervous" and "malignant" fever were separated. It is interesting to note that John Hunter had two specimens showing the characteristic intestinal lesions.

It was in France that the first great advance was made, largely through the more careful study of pathological anatomy, and early in the nineteenth century there were many important observations. Prost (1804) noted the characteristic intestinal lesions which Broussais designated as "Gastro-Entérite" but they did not distinguish them from the conditions found in enteritis. Petit and Serres in 1817 described the ulcers in the intestines as specific and analogous to the lesions of smallpox, regarding them as an internal exanthem. They used the term "Fièvre mésentérique" and held that this was a definite disease. Bretonneau, who studied an epidemic in

Tours, suggested the name "Dothienentérite," which has been extensively used in France. He recognized that the Peyer's patches and solitary follicles were specially involved. Trousseau and Velpeau studied under Bretonneau, and when they went to Paris carried his views with them. In 1829 the work of Louis appeared, in which the features of the disease were described, the constancy of the lesion shown and the term "Fièvre typhoïde" suggested. It is doubtful if Louis himself regarded the disease which he described as typhoid fever as in any way different from the disease in other parts of Europe, which in many instances was typhus fever. The general opinion was that the disease associated with lesions in the bowel was only a variety of the common continued fever. At this time the prevailing continued fever in France was typhoid fever, while in England typhus and typhoid fever co-existed. The French writers, seeing only the one disease, thought that characteristic intestinal lesions would be found in all cases of the disease known as putrid fever, jail fever, etc. (typhus), but this was found not to be the case and naturally much difference of opinion resulted. The French and English physicians were discussing two distinct diseases under the same name. Looking back it can be seen that where the observer had the opportunity of seeing typhoid fever alone he arrived at fairly clear views of its essential features, but where the two diseases were prevalent there was much confusion and the intestinal lesions were regarded as being present occasionally in some of the cases. About the same time some writers grouped these various fevers under the term "Krankheitsfamilie Typhus," which can not have aided the solution of the difficulty.

In Paris at this time there was an epidemic of typhoid fever which was carefully studied by Louis. Among his students was W. W. Gerhard of Philadelphia, who thus had excellent opportunities for the observation of the disease. On his return home he recognized the continued fever then prevalent in Philadelphia as identical with the typhoid fever of Louis which he had seen in Paris. In 1835[1] Gerhard reported these observations, but from his paper it is doubtful if he had a clear idea at that time of the distinction between typhus and typhoid fevers. He recognized that in the disease under observation there were intestinal lesions and that it was the same that he had seen with Louis in Paris. However the opportunities of the next year put the matter beyond doubt, for in 1836 there was an epidemic of typhus fever in Philadelphia, and as Stillé says of Gerhard, "he may be said to have been the first to meet the two diseases face to face with a full acquaintance of one of them and a daily increasing knowledge of the other." In the report of this epidemic, published in 1837,[1] he sets out very clearly the distinction between the two diseases as well as their differentiation from malarial fever. This paper should be read by every student of the disease, for it is the first in which typhus and typhoid fevers are clearly distinguished and thoroughly contrasted.

To other American students much credit is due for the spread of these opinions. Alfred Stillé had worked under Gerhard in Philadelphia during the typhus epidemic of 1836 and afterward went to Paris, where he studied typhoid fever under Louis. In London, Edinburgh, Dublin and Naples, he saw typhus fever and thus had an excellent opportunity to appreciate the differences between the two diseases. In 1838 he read a paper before

[1] *The American Journal of the Medical Sciences,* 1835 and 1837.

the Medical Society of Observation of Paris entitled, "Table of Comparison between Typhus and Typhoid Fevers," which was not published at the time but has been brought out recently in the *University of Pennsylvania Medical Bulletin* for 1904. Another American student of Louis was G. C. Shattuck of Boston, who, familiar with typhoid fever in Paris, went to London and immediately recognized that there were two distinct diseases there which were not separated by the English physicians. He also presented his conclusions before the Society in Paris. It seems altogether probable that these papers of Stillé and Shattuck had considerable influence on French opinion. In Boston, James Jackson, Jr., after his return from Paris, had shown the identity of the common continued fever there with the typhoid of Louis. Papers on typhoid fever were published in Boston in 1838 and 1839 by James Jackson, Sr., and Enoch Hale. It is worthy of mention that in 1824 Nathan Smith published a description of typhoid fever. He did not distinguish between the two diseases for he evidently saw only one, but his description stands as one of the classics of American medicine and is one of the best early accounts of the disease. It should be read by everyone interested in typhoid fever. He refers to the fact that the disease appeared in New England very soon after the first settlements.

The new views gained acceptance rapidly and the clear distinction between typhus and typhoid fevers was earlier and more generally recognized in the United States than in any other country. Elisha Bartlett in 1842 published the first treatise in which the two diseases were discussed separately. In Britain about this time very confused views were held, for the two fevers were prevalent and the intestinal lesions were regarded as accidental occurrences in certain of the cases. Bright in 1827 very clearly described the morbid anatomy of the bowel lesions, but there is no proof that he had a definite idea of the distinction between the two diseases. He protested against the treatment of the continued fevers by purging. Their non-identity was first established in Britain by Stewart, who studied typhoid fever in Glasgow in 1836–38 and published his observations in 1840, presented as a communication before the Parisian Medical Society. It was really not until the work of Jenner in 1849–51 that the question was settled in England. The old ideas died slowly and the Irish physicians especially held tenaciously to the view of the identity of the fevers even as late as 1861.

Meanwhile Schönlein in 1839 proposed the name "Typhus abdominalis," which has been so extensively used in Germany for typhoid fever, and "Typhus exanthematicus" for typhus fever. Louis in 1841, in the second edition of his work, emphasized the non-identity of the two diseases. From 1840 to 1850 there were many students of the disease, and Griesinger in Germany, with Murchison and Jenner in England, did much to spread the new doctrines. Murchison designated the disease "pythogenic fever" but fortunately this was not generally accepted, as it involved erroneous views as to the etiology. Wilks suggested the term "enteric fever" or "enterica," which has been widely adopted in Great Britain.

After the identity of the disease was established there were many theories as to the mode of infection. It would have been strange if during the time that typhoid fever was confused with other diseases there had been any clear ideas as to its etiology After its separation as a distinct disease, explanations for its spread were immediately sought, and some of these contained a certain amount of truth, although partly based on erroneous

ideas. It was early noted that there was comparatively slight danger of direct infection from the patients with typhoid fever, although instances of house and hospital infection were observed. These led some of the French clinicians to consider that the disease was capable of transmission through the air or by direct contagion, and although the reasons which led to this view were not correct, yet, as we have learned recently, to some extent their conclusions were right. But at that time by far the greater number of authorities considered that the important factor in the transmission of the disease was some process of decomposition or putrefaction, while some held that under these conditions the disease might arise *de novo*. Murchison was one of the first to suggest that the contagion was carried by the fæces, but this he regarded as occurring after putrefaction of the excreta, and then water, food or air might be contaminated and infection result. Much importance was attached to impure air or sewer gas as a source of infection, an idea which is still strongly held in some quarters. While many of these ideas were wrong, yet in the main they were correct in considering that the chief source of infection was in the discharges from the patient.

The man who first published clear views as to the mode of infection was Budd of Bristol, whose papers are in the *Lancet* (1856–60). He believed that the infective agent was in the stools of the typhoid fever patient and that the disease never arose spontaneously but always from a specific source. He held that a previous focus was necessary before a neighborhood could be infected and by the study of many epidemics recognized the result of the introduction of infection into a community and noted that a few straggling cases at first might be followed by a larger outbreak. He considered that a minimal amount of the infective material was able to convey the disease, and arguing from these beliefs he put forward the view that the possibility of infection could be prevented if the stools were thoroughly disinfected. His views are essentially correct, and Budd may be regarded as the first to recognize the leading points in the transmission of the disease. But the ideas as to the influence of decomposition and local conditions were firmly fixed, and the endemic occurrence of the disease, its persistence in some localities and its association with defective drainage, all fixed men's minds on the soil and not on the patient as the source of infection. This was specially developed, as regards one condition of the soil, in the "ground water" theory of Buhl and Pettenkofer (1865–68). They considered that a definite association existed between the height of the ground water and the prevalence of typhoid fever. When the ground water was low typhoid fever was prevalent. Their conclusions were based largely on local conditions in Munich and failed to take account of other factors. This theory was widely accepted, especially in Germany, and with it other ideas became associated. The infective agent was thought to undergo some change in the ground and its conveyance to be frequently through the air. These views, however, did not obtain universal acceptance and were strongly opposed by Liebermeister.

In 1880 Eberth discovered the specific cause of the disease, and Gaffky a few years later extended the knowledge of the special morphology of the *B. typhosus*. Although neither of these observers was able to produce the disease experimentally, yet the organism was accepted as the cause of typhoid fever. After the recognition of the bacillus our knowledge of many points connected with the mode of infection and of certain features of the

disease increased rapidly. The discovery of the agglutination reactions opened a wide field for research and in 1895, following the work of Pfeiffer, Gruber, Durham and Grünbaum, the reaction was specially brought into clinical application by Widal.

ETIOLOGY.

"The effect of what are usually regarded as the most common exciting causes of many forms of disease. . . . is not very obvious in the production of typhoid fever."—Elisha Bartlet.

The typhoid bacillus is the essential cause of the disease, but the means by which it gains admittance to the body are very various. These "intermediary bodies," however, are only carriers, for the bacillus is dependent on man for its existence, and although it may live for a time in water or on various articles, yet its life in such situations is comparatively short. Man is the cause of the continuance of the disease but there are many factors which influence the conveyance of bacilli from one individual to another.

Geographical.—Typhoid fever is one of the most widespread of the infectious diseases. It occurs in the tropics and in far northern and southern latitudes, at sea-level and in the mountains, in the city and in the country, and practically wherever man may go and local conditions do not prevent the dissemination of the disease. The *B. typhosus* has about the same limits of latitude and longitude as man himself, and no country or race is known to be immune from the disease. The character of the water-supply and the means of disposal of excreta must be regarded as the most important factors which influence the occurrence of the disease in communities, while filth, bad hygienic conditions and overcrowding have a certain effect. When men are living together under unusual conditions, such as an army in the field, other factors appear and have an important influence. But under any conditions or climate the essential thing which governs the occurrence of the disease *is the method in which the excreta are disposed.* Given the occurrence of typhoid fever other factors become active, but as a rule the statement stands that "the history of this disease justifies us in stating that wherever and whenever men congregate and live together without adequate provision for disposing of their excrement, there and then typhoid fever will appear."

The careful study of the bacillus and of the causes of epidemics has greatly increased our knowledge of the influences at work in the spread of the disease, and we owe much to recent wars for extending our information on many points. In this connection the report of the Commission for the Study of Typhoid Fever in the Spanish-American War (Reed, Vaughan and Shakespeare) is especially valuable and is one of the best contributions to our knowledge of the disease. The importance of increasing our knowledge of the conditions which have determined epidemics is very great. The source of many infections has been properly determined; in many cases this is too late to be of much use as regards that particular outbreak and unfortunately as a people we seem rarely able to improve the future by the lessons of the past.

There may be marked differences in the character of the disease in a community from one year to another. It has long been noted that a new-

comer, if he contracts the disease, is likely to have a more severe attack than the average of the residents. This is especially true in cities, and Trousseau laid emphasis on it in Paris. The patients at the beginning of an epidemic may show marked differences in the severity of the attacks from those seen subsequently.

Typhoid fever differs in its method of spread from the acute infectious diseases. It does not extend over a continent as influenza, nor does it strike the majority of those exposed to it as smallpox or measles in an unprotected community. It travels in a more insidious manner, as shown in an epidemic described by Briggs. One man visits Pittsburg and contracts the disease. He returns to an eastern town and in a few days comes down with a typical attack, being ill from January 26 to March 4. From his excreta the local water-supply is infected and 45 cases result. The distance from Pittsburg was great in miles but measured by generations of typhoid bacilli the interval was small. The disease may be contracted in Europe and carried to the United States during the attack itself, or if we consider the length of time during which typhoid bacilli may remain in the urine, it is no exaggeration to say that a man may scatter infection around the world.

Fulton has shown that typhoid fever in the United States is a disease more prevalent in rural communities than in cities. The census of 1900 showed that in the registration areas the mortality per 100,000 population was slightly greater in the rural districts than in the cities (25.5 to 25.3). Rural typhoid was credited with 62 and urban typhoid with 38 in every 1,000 deaths. "Typhoid mortality rises as population density decreases, down to a population of 50 per square mile" (Fulton). He quotes Maryland as an example, which has one large city comprising about half the population of the state, and yet the ratio of typhoid mortality is 1 to 2.5 in favor of Baltimore, although its water-supply is unfiltered and obtained from an unprotected watershed. This rural frequency is important for dwellers in cities. The water- and milk-supply, as well as many articles of food, are derived from the country. There is a constant going and coming between the city and country. An infected city may spread infection far and wide through the country, while from the country there may be a steady stream of infected persons into the city. This is well seen in Baltimore, where many persons contract the disease by drinking the water of small villages in the surrounding country.

War.—As has been said, an army has two foes—"bacilli and men," and of these the former is by far the more dangerous. It is not possible to recognize with any certainty the nature of epidemics which visited armies earlier than the latter half of the nineteenth century, but some of the accounts suggest typhoid fever. Thus in the Civil War in England the descriptions are usually regarded as of this disease. In the campaigns in the Netherlands there was much sickness from a fever which was prevalent among the natives in the autumn. In the wars of the last fifty years typhoid fever has played an important role. In the American Civil War there were in the northern army 75,361 cases among the white troops with 27,056 deaths, and 4,094 cases among the colored troops with 2,280 deaths, while the large percentage of deaths suggests that there were probably many more cases of the disease than were recognized. In the Franco-Prussian War of 1870–71, among the German troops there were 73,396

cases of typhoid fever with 8,789 deaths, which comprised 60 per cent. of the total mortality. The incidence in proportion to strength in the German army was very high. There was typhoid fever in every corps of the army at the beginning of the war and two factors influenced the prevalence of the disease,—the troops carried infection with them and were campaigning in a country in which typhoid fever was common. In the Spanish-American War the highest incidence of typhoid fever was among the troops who never left the United States. Among 107,973 men there were 20,738 who had typhoid fever, with 1,580 deaths, a rate of 14.6 per 1,000 of mean strength. It was found that 90 per cent. of the volunteer regiments had men with typhoid fever within eight weeks after going into camp and that epidemics were as marked in the North as in the South. With the ordinary incidence of the disease, any body of 1,000 men taken from private life and kept together for two months will have one or two cases, while the number of subsequent cases in any corps varies with the method of the disposal of the excreta.

In the South-African War,[1] the British Army had 31,118 cases of typhoid fever with 5,877 deaths. There were 7,582 deaths from wounds and 5,149 from other diseases. While infection may have been carried by the troops in some cases yet the chief source was from the Boers. At Paardeberg they contaminated the water-supply and the British troops became infected. In a few days they reached Bloemfontein where a large army was collected; the troops were crowded together and the element of personal contact, shown to be so important in the Spanish-American War, began to operate. From Bloemfontein the troops marched to Pretoria and were then scattered to various districts. Thus the disease was carried in every direction, there was constant meeting and re-meeting of regiments, and the same camping grounds were used for successive corps. Frequently the troops camped on farms where there had been typhoid fever. Added to these factors were the local conditions, especially as regards the water-supply and sand. The country being poorly supplied with water the population lived near the streams, and surface water was often all that was available. Dust and sand were perfect plagues and must have been one means by which typhoid bacilli got into the food and drink. Flies also were numerous and doubtless played an important part.

The importance of the "auto-infection"—if the term may be used—of an army with typhoid fever is well brought out by the results of many campaigns. Thus in the Afghan War of 1878–80, the British troops brought the disease with them from infected areas in India, and it was carried to localities where previously it was unknown. In the Suakim expedition of 1885, all the drinking water was distilled, yet they had typhoid fever, probably carried by one infected regiment. In the Egyptian War of 1882, certain regiments carried the disease with them, while other regiments, which entered the same campaign free from typhoid fever, escaped, despite the fact that they drank bad water. In the Chitral campaign of 1895, typhoid fever was carried in by the troops. There was a marked difference in the occurrence of the disease among the privates and officers, the latter escaping almost entirely. The men were much more crowded together, the close contact favoring infection, and this is thought to have explained the relative immunity of the officers.

[1]The published figures vary slightly; the official returns are not yet available.

It is evident that the problem of etiology differs somewhat in civil and military life. There are several factors in this: (*a*) The greater difficulty in disposal of the excreta. Only those who have handled men in camps know the difficulty of making them observe sanitary regulations, either defective or perfect. This, and the difficulty of disposing of excreta, lead to infection in various ways, as the water-supply may be contaminated, the bacilli blown about with dust or carried by flies. (*b*) The close contact of men crowded together in tents favors direct infection, while clothing, blankets and tents may all become soiled and contaminated. The influence of camp life on troops who had a good water-supply was well shown at Jacksonville, Florida, in the fall of 1898. There were about 30,000 people in the city with very few cases of typhoid fever, while among the troops near by, with the same water-supply, the disease was very prevalent.

Season.—As a rule the disease shows a fairly uniform relation to the time of the year, in Europe and America being most prevalent in the autumn months. Of the 1,500 cases of this series,[1] 840 (56 per cent.) were admitted in the months of August, September and October. The disease usually persists on into the winter months, with a decrease after December, the smallest number of cases occurring during the spring months. But in the majority of the American cities there is a certain prevalence throughout the year, no month being without a few cases. Epidemics may occur at any season if there be infection of the water-supply, and in some instances this has happened early in the spring from bacilli being carried into streams or reservoirs with the melting of the snow.

It does not seem that we have any satisfactory explanation for this seasonal variation. It is so general and occurs apart from local conditions with such regularity, that some condition associated with the development of the typhoid bacillus must be concerned. The disease is likely to be especially prevalent in hot and dry seasons, but the contrary is not necessarily true. It may be that the state of the ground water has some influence, as when this is low the sources of the water-supply are more likely to drain a wider area and thus the chances of infection be greater. This probably applies especially to rural districts. It may be that in dry seasons there is more possibility of the bacilli being carried about with dust. There is also a great increase in the number of persons who are exposed to infection during the summer months. People from the cities spend their vacations in the country where there is usually much more chance of infection.

Sex.—There does not seem any reason why one sex should be more subject to the disease, unless the more active life of men gives greater chances of infection, but almost all hospital statistics show a larger proportion of males. In this series, 1,062 were males and 438 females (2.4 to 1), the usual ratio of admissions in the whole clinic being about 5 males to 4 females. It is easy to understand why females should always be fewer in hospital statistics, yet even in statistics of the disease in childhood, there is usually a preponderance of males.

Age.—The disease is one especially of youth and early adult life and in this series the incidence was:

[1]This article is based on the experience of the Johns Hopkins Hospital series of 1,500 cases and 105 autopsies.

	Number	Per Cent.
Under one year	2	0.013
1 to 15 years	231	15.
15 to 20 years	253	17.
20 to 30 years	680	45.
30 to 40 years	227	15.
40 to 50 years	88	6.
50 to 60 years	8	0.5
60 to 70 years	11	0.7

Among 19,586 cases in the London Fever Hospitals from 1871 to 1904 the distribution was: Under 5 years, 3.4 per cent.; 5 to 10, 13 per cent.; 10 to 20, 41 per cent.; 20 to 30, 26 per cent.; 30 to 40, 11.6 per cent.; 40 to 50, 4 per cent.; 50 to 60, 0.8 per cent.; and over 60, 0.2 per cent. During the first year of life the disease is rare, and there is then a gradual increase up to about the fifteenth year, from which age up to forty the disease is most prevalent. After forty the number gradually diminishes but it is by no means infrequent even in old age.

Constitution and Mode of Life.—As regards the bodily condition there does not seem any proof of the correctness of the popular idea that an attack of typhoid fever means a previously "run-down" condition; on the contrary it is often those in the best physical state who contract the disease. The social surroundings do not seem to play much part. The water-supply of the community is usually much the same for rich and poor. Given, however, a case in a household and the chances of infection of other members are greater among the poorer classes, where crowding is more common and isolation and disinfection are likely to be less efficient. As regards occupation, there does not seem to be any special peculiarity, except in active military service. Barringer states that typhoid fever is very prevalent among the trackmen on railroads. Physicians and nurses who are handling patients with the disease are in some danger of infection, even with care. Cold and fatigue cannot be regarded as having any etiological influence and probably the former is often the interpretation of the early chilly sensations, the latter really the first symptom noticed by the patient.

Gastro-intestinal Conditions.—That gastric conditions may have some influence may be thought probable but is not proved. On general grounds a normal gastric juice should afford more protection than one deficient in acid and ferments, but the typhoid bacillus is probably not destroyed by ordinary gastric juice. Some writers have held that many patients have a dilated stomach, which favored infection, or that the secretions were altered. As regards gastro-intestinal disturbances, the studies of the Spanish-American War Commission show that these do not predispose to typhoid fever. Thus, of 9,481 men who had previous diarrhœal attacks only 648, or 6.8 per cent., had typhoid fever, while of 46,348 men who had no preceding diarrhœa, 7,097, or 15.3 per cent. had the disease, and more than 90 per cent. of the typhoid fever patients had no preceding intestinal disorder. Guiart of Paris has suggested that wounds of the intestinal mucosa made by whipworms may be the points of entrance of the bacilli.

Certain conditions are thought to confer relative immunity, among which are pregnancy and the puerperal state. This is difficult to decide from statistics, as the figures usually given include females of all ages. Women who are pregnant may possibly be less likely to be exposed to infection,

In the present series, among 438 female patients there were 6 who were pregnant. Taking the figures of Curschmann, Goldammer and Martinet with this series, among 3,355 female patients there were 93 who were pregnant (2.8 per cent.). In the puerperal state and during lactation the disease is rare and there were only 2 instances in this series. Other diseases, such as tuberculosis and the acute exanthemata, are thought to give immunity, but this seems doubtful when the number of instances of the co-existence of typhoid fever and these diseases is considered. Chronic nervous maladies and malignant disease cannot be considered as giving immunity.

Modes of Infection.—These are numerous, and while in a sudden epidemic it may be possible to determine the source of infection with certainty, in the steady endemic occurrence it may be very difficult. Take any ordinary community with its usual number of cases every year, and in many of these the source of infection cannot be determined positively. One thing we are sure of—the bacilli came from another patient, the moral of which is obvious.

1. **Direct Infection.**—This is probably much more frequent than has been supposed. In armies, or wherever a large number of persons are crowded together, it is a prominent factor. It also occurs to a considerable extent in houses, especially where there are crowded conditions. Those associated with or waiting on the patient may be careless and carry the bacilli on their own hands to the mouth, or infect the food. Probably those nursing a patient always get some bacilli on the hands and without great care others may be infected. In a case reported by Dudgeon and Gray, a woman was apparently infected by handling the soiled dressing from a typhoid bone lesion in her husband's leg, the pus from which contained typhoid bacilli in pure culture. The more carefully epidemics are studied the more often will cases of contact infection be found. Among the last 500 patients of this series, there were 55 who came from houses in which were other patients with the disease, and in many instances they had been nursing the patients before becoming sick themselves. Doubtless some of these contracted the disease from the same source as the first patient, but in many the probability is strong of more or less direct infection having occurred. During the same time there were 7 trained nurses who had been nursing patients with typhoid fever outside the hospital and 5 who were nursing in the wards. There was 1 worker in a laboratory who was handling typhoid bacilli and 1 orderly waiting on patients with the disease. This gives a total of 69 out of 500 who were exposed to more or less direct infection. During the same period there were 8 patients whose infection could be associated with small epidemics arising among those who had used the same water (those using the city water-supply are not included). That contact infection does not always play much part is shown by the report of Smith on the conditions in Belfast, where from 1898 to 1903 there were 12,900 cases of typhoid fever in 11,017 houses, that is, in 85 per cent. there was only one case to a house.

The influence of contact is especially shown where large numbers of men are collected together, as in a camp of Boer prisoners in the hills of Ceylon, in which over 5,000 men were collected. The locality was high and the water-supply good. The camp was free of disease until typhoid fever was introduced by some newly arrived prisoners. Within three months there were over 700 cases among the prisoners; the troops guarding them, whc

were under practically identical conditions as regards food and water-supply, escaped entirely.

Even in hospitals there is some danger, despite all precautions. Schuder has estimated that 3.3 per cent. of all cases are due to hospital infection. It is stated that from 1881 to 1889, of the cases in the German army, 6.3 per cent. were from hospital infection. Dubus collected 145 instances among 5,989 cases (2.4 per cent.). It is especially likely to occur if a hospital is unduly crowded so that the wards have to accommodate more patients than usual. In this clinic there have been 31 instances of infection occurring in persons in the hospital. Of these 5 were physicians, 3 of whom were in the medical wards, the others being on the surgical staff. There were 15 nurses, of whom 11 had been nursing patients with the disease. Of the 8 patients, 3 were in surgical wards and not in contact with patients who had the disease. Four cases among patients occurred in a ward epidemic. There were 2 orderlies, both of whom were working with typhoid patients, and it is difficult to understand why so few of them have been attacked, as they are often careless, despite watching.

There is great danger of direct contagion in children's hospitals, especially if the beds are very close together or the convalescents are allowed to play with other children. Dubus[1] mentions one hospital in which there were 27 instances of direct contagion in three years. In many of these the disease was contracted by a child in the bed next to the patient with typhoid fever. If the children are bathed in the same tub the danger is increased, as is shown in the report by Bloch[2] of an epidemic of typhoid fever which occurred in a scarlet fever pavilion, 13 patients being infected. The possibility of infection from water or milk was excluded. It was noted that female patients only were infected, and it was found that almost all had a gonorrhœal vulvovaginitis. Suspicion was then directed to the method of bathing and it was found that the children had been bathed in one tub and the same cloths had been used for several patients, while the attendants had not been careful to clean their hands after attending to each patient. From the pus from the vagina of two of these patients typhoid bacilli and gonococci were obtained. It was supposed that the bacilli were conveyed from one child to another by the cloths or bath water and then carried to the mouth by the hands. The primary source was a patient admitted with the disease. The epidemic ceased as soon as the patients were rigidly isolated. Of all the children exposed, 26 per cent. were infected, but during the time when probably the infection was carried, 52 per cent. of those exposed contracted the disease.

2. **Water.**—This must be regarded as an important means of conveyance and in large epidemics, where the extent is influenced by the amount and freshness of the infection, it usually plays a large part, as well as in the yearly incidence in many communities. Schuder, in the study of 638 epidemics which occurred from 1870 to 1899, found that the infection was carried by water in 71 per cent. There are very few definitely proved records of the recovery of typhoid bacilli from drinking water, but in many instances the time of infection has antedated the time of culture. Willson, who has recently reviewed the subject, considers that only 6 instances of the recovery of typhoid bacilli from drinking water can be regarded as definitely proved.

[1] *Thesis*, Paris, 1905.
[2] *Ibid*

In the sudden outbreaks it may be very easy to trace the source of infection to the water-supply, for such epidemics are often "explosive," but in places where there is only the usual number of cases this may be difficult. It is probable that by improved cultural methods our knowledge of the life of typhoid bacilli in water will be greatly increased. The amount of light, organic matter and oxygen are important. The possibility of multiplication of the bacilli in water under favorable conditions is not positively determined.

The steady decrease in the disease in communities as the water-supply is improved is perhaps one of the best proofs of the importance of water-borne infection. In Hamburg from 1885 to 1888 there were 15,804 cases of typhoid fever. The water-supply was taken from the Elbe, not far from the point where the sewers discharged. The neighboring city of Wandsbeck, with a separate water-supply, was almost free from the disease, giving a demonstration as striking as that of Altona in the cholera epidemic of 1892. In Paris, with a better water-supply, the death-rate from 1882 to 1902 was reduced from 142 to 17 per 100,000. It has to be kept in mind that a polluted water-supply is not a source of infection unless the *B. typhosus* be present. There have been cities which used a greatly polluted water and yet had a low typhoid rate. The outbreak in Plymouth, Pa., in 1885, is one of the most instructive examples of an epidemic due to an infected water-supply.[1] This was a town with 8,000 inhabitants and not in a very good sanitary condition. The water-supply was largely derived from a stream, on the watershed of which were only two houses; a small part of the town used water pumped from the Susquehanna river and those who used this supply escaped. The general supply came from a mountain stream on which four storage reservoirs had been built. On April 9th, typhoid fever appeared in Plymouth, and in a few days there were from 50 to 100 new cases a day, and the total number was 1,104. The possible sources of infection were investigated and all suspicions centred on the water-supply. It was found that in the house on the stream between the third and fourth reservoirs there had been a patient ill with typhoid fever. He contracted the disease away from home and was sick on his return on January 2d. Early in March he was convalescent and then had a relapse with hemorrhages and was very ill about the middle of the month. The stools passed during the day were emptied into a privy, the contents of which lay almost on the ground, which sloped toward the stream. At night the stools were thrown either into the stream or on its banks. The stools in the privy and on the bank lay on the snow and frozen ground until the last week in March, when came unusually warm weather and a thaw, with which the material on the surface was washed into the stream and then into the third reservoir. On March 26, it was found that the first and second reservoirs were nearly empty and that the pipe leading from the third to the second reservoir was frozen. A fire was lighted to melt the ice and so the water in the third reservoir, infected by the accumulation of the excreta of the typhoid patient from January 2d, was let through and passed rapidly into the town, as the lower reservoirs were nearly empty. It can thus be seen that the water-supply was very heavily infected. It is said that the

[1] This was studied by committees from New York, Philadelphia, and Buffalo. An excellent report was published by Taylor.

physician attending the patient who was the source of infection did not know that the stream supplied the reservoirs, but at any rate no attempt had been made to disinfect the excreta.

Ice has rarely been proved to be the means of conveyance of typhoid bacilli, although frequently under suspicion. The report of an epidemic due to ice at the St. Lawrence State Hospital, near Ogdensburg, N. Y., is given by Hutchings and Wheeler. The institution had been free from typhoid fever for some time when, early in 1903, they had an epidemic of 39 cases. Six days before the appearance of the first case, ice from a new ice-house had been used. This had been filled in February by ice taken from the St. Lawrence River three miles below Ogdensburg, in which city there had been typhoid fever. The sewage from Ogdensburg was emptied into the river above the point from which the ice was gathered. In the ice there were masses of foreign matter and sediment, in which motile bacilli were found, and typhoid bacilli were grown in cultures from these. The epidemic subsided as soon as the use of this ice was discontinued.

3. **Food.**—(*a*) *Milk.*—There have been many epidemics in which all the evidence pointed to milk as the source of infection. Schuder, among 638 epidemics, found infected milk to be the cause in 17 per cent. In many of these it is not possible to obtain direct bacteriological evidence, but the facts are so suggestive as to be almost conclusive. When the disease is confined to the users of milk from one farm and there is strong probability of infection from a patient, there seems little doubt of the proof. In other cases the infection may occur during the transfer of the milk in the city, either in the establishments which handle it or in small distributing stores. Creameries have been the source of infection in some instances.

An epidemic in Palo Alto, California, in 1903, was traced to infection through milk (Fish, Mosher and Snow). Among 900 people who obtained milk from the same supply, 232 had typhoid fever; of these, 216 were apparently due to infection from the milk, while 16 may have been due to secondary infection, although all but two used the infected milk. That is, 98 per cent. of the typhoid fever patients had used the one milk-supply and 26 per cent. of the users of this supply had typhoid fever. The milk-supply was evidently infected for the month of March, the onset in the majority of the patients being in the first half of April. It was found that the water used for washing the cans and also at times for diluting the milk was obtained from a creek which was infected by the drainage from houses in which there were patients with typhoid fever. The original infection had apparently been brought in by visitors. Cultures from the milk and from the water used for washing the cans yielded the colon bacillus.

It may be difficult to trace the exact source of infection but there are probably more instances than are generally supposed of infection of milk in small stores and milk depots. Should there be a patient with typhoid fever in the same building it can easily be seen how the milk may become infected by the same person waiting on the patient and handling the milk. Such infection may be responsible for small local epidemics, but in the majority of instances of infection by milk this is secondary to infection of the water used for cleaning the cans The amount of milk taken probably influences the chance of infection. Thus, in the Palo Alto epidemic a larger percentage of patients was found among those who had two deliveries of milk a day, and presumably used more, than among those who had one.

Ice-cream may be a source of infection, the process of freezing not killing the bacilli. Such a means of infection might be very difficult to trace, but it is probably not infrequent and an instructive epidemic is reported from Govan by Barras. In five days there were 19 patients with the disease, all of whom had eaten ice-cream from one store. It was found that the proprietor of the shop had been ill for ten days with what he supposed was influenza but which proved to be typhoid fever. During this time he had assisted in the making of the ice-cream. The milk-supply was excluded as a cause.

Butter and Cheese.—It is doubtful if these are frequently a source of infection. Typhoid bacilli may live for a varying period in butter, some observers giving as long as 27 days, but in these experiments the butter receives a heavy inoculation under conditions favorable for the organisms. Under ordinary conditions their duration of life is not likely to be long, owing to the number of vigorous saprophytes, the chances of being washed out with the buttermilk (as happens to nine-tenths of the bacteria in the cream), and the salting. The danger of infection from cheese must be practically *nil*, owing to the long period of ripening.

(*b*) *Shell-fish.*—There are a considerable number of instances of infection by these. In this country oysters and clams are most frequently under suspicion, and in England mussels and cockles have also to be considered. It may be easy to prove that they have carried infection if there be an epidemic, but it is likely to be very difficult in sporadic cases. Shell-fish may be sent to considerable distances and widely distributed; hence the cases are not so likely to be associated as in a milk epidemic. One of the first epidemics traced to infection by oysters was that in Middletown, which was studied by Conn. This occurred among students and at first it was difficult to find any common source of infection. Investigation showed that this could only have been from oysters which had been eaten at several dinners on the same evening. It was found that these oysters had been put into a small creek, for the purpose of "fattening," within one hundred yards of the outlets of a number of sewers, one of which came from a house in which there were two patients with typhoid fever. Infection of students in another place followed the use of oysters from the same supply. In England there have been many instances; thus, after a banquet at Winchester 62 among 134 guests were ill, and of these 11 had typhoid fever, and at Southampton 55 out of 132 were ill and 11 had typhoid fever. All of those who became ill had eaten oysters.

In all shell-fish, the danger comes from the water in which they are put, either for "fattening" or until they are wanted for use, as for convenience they are likely to be kept near the shore and consequently in water which is contaminated. Oysters taken from these feeding grounds in rivers or inlets contain a much larger number of organisms than those directly from salt water away from the shore. If the oysters become infected, typhoid bacilli may live in them for some days, but there is no evidence that they multiply and after a certain time they tend to die. If the contaminated oysters are put in clean water, especially if it be salt, the bacilli disappear in a few days. The bacilli do not die in mussels as rapidly as in oysters, and there is some evidence to show that in them there may be multiplication of the organisms. Klein has worked on this subject and has obtained typhoid bacilli from oysters in three instances and from mussels once. There

have been many investigations as to the distance at which bacteria may be found from the outlets of sewers. Thus Fuller found the colon bacillus in 40 per cent. of oysters and 70 per cent. of the samples of water taken five miles from a sewer outlet.

Dried fish have apparently carried the infection, as in a small epidemic in London in which many of those infected had eaten improperly cleaned fish from one shop.

(*c*) *Vegetables.*—These are carriers of infection only when eaten in the uncooked state. The danger of infection may be from the vegetables having been grown on land which has been fertilized by infected material, the water used in washing them may be infected, or the bacilli may be carried on the hands of those preparing or handling them. In Hackney, London, there were two local outbreaks in which it was found that a large proportion of the patients had eaten water-cress. Cultures from samples of this showed sewage organisms and colon bacilli. When vegetables are exposed for sale there may be a possibility of bacilli being carried with dust and deposited on them.

(*d*) *Beer.*—That bacilli may be taken in with beer is possible but not probable. Suremont found that the bacilli did not live longer than three days in beer.

4. **Flies.**—Much evidence has been brought forward of late to show that flies are frequent carriers of infection, and there can be no question of the proof. They may carry the bacilli in one of two ways: the infected material may cling to the fly and be deposited on the food, or the bacilli may be swallowed by the fly and deposited later. Fischer estimates the duration of life of typhoid bacilli in the bodies of flies as twenty-three days. They can live for some days on the head and legs of flies. Firth and Horrocks showed that flies could carry the bacilli from infected material and deposit them on culture media.

Flies were important agents in the transmission of the disease during the Spanish-American War. They settled on infected fæcal material and later on the food. In camps, where lime had been used to disinfect the privy pits, flies with their feet covered with lime were seen walking over the food. The disease was less prevalent among regiments who had the mess tents screened. With the decrease in the autumn of the number of flies, the number of cases lessened, and this at a time when as a rule the disease is on the increase. In the South African War flies undoubtedly played a large part in the transmission of the disease. They were very numerous and it was noted that there were large numbers about the typhoid fever patients. When cold weather came there was a great decrease in the number of cases.

In an epidemic in Chicago in 1902 the number of patients in one district with poor sanitary arrangements was unduly large, and Alice Hamilton found that this was due to infection carried by flies. In many yards in this district there was fæcal material exposed only a short distance from the houses. Flies were caught in the privies, on the fence near by and in the sick-room of a house, and tubes inoculated from them. In several of them (5 out of 18) typhoid bacilli were found, and in one the organism belonged to the group intermediate between the typhoid and colon bacillus. An epidemic in the jail at New Haven was thought to be due to infection carried by flies from patients across the street.

Many of the instances of the spread of the disease in rural communities are probably due to flies. It is easy to understand how the dwellers in an ordinary farmhouse can be infected, especially if the excreta are not carefully disinfected. The convalescent with bacilli in his urine may be an especial source of danger. Even under good sanitary conditions and with disinfection flies may carry infection, for it is often noted that certain typhoid fever patients attract flies, and it may be possible for them to pick up some bacilli, which are thus carried and infect food. It may be that some of the instances of hospital infection are to be thus explained.

5. **Dust.**—This may be a factor under certain conditions. Typhoid bacilli soon die if desiccated, but if the interval be short they may survive. Thus in the South African War there were frequent dust storms in some localities, so that the food was covered with dust and sand. It is easy to see that bacilli deposited on the surface of the soil could readily be carried and so infect food. Barringer has suggested that the dust on railway tracks may be an important factor in the spread of the disease, as there is much opportunity for infection by excreta dropped from the trains. This dries, and the bacilli may then be blown about with the dust. Typhoid fever is said by him to be very prevalent among the trackmen on railroads. Infection of water along the track may also be a factor.

6. **Clothing.**—Under usual conditions of life, instances of infection being carried in this way are rare. Those handling soiled linen which has not been properly disinfected may contract the disease. It is, however, when men are crowded together, as in barracks or camps, that clothing is a common carrier of infection. This was specially brought out in the Spanish-American War, in which clothing, blankets and tents became infected. Epidemics in barracks have been reported which seemed to be from infection of the clothing. After the South-African War, blankets which had been used by the troops were sold, contrary to regulations, and sent back to England. Some of these were used in a training ship, on which typhoid fever appeared. On investigation the blankets were found to be dirty and soiled with fæcal material; Klein is said to have obtained living typhoid bacilli from these areas.

The matter has an important bearing on the care with which we should disinfect the rooms and bedding used by typhoid fever patients. As a rule this is not done with any thoroughness, although some writers insist that it should be carried out as carefully as after scarlet fever. There is no doubt that typhoid bacilli can live for some time on clothing.

7. **Conditions in the Soil.**—Long regarded as the most important factors in the spread of the disease and in fact considered an essential element, we now consider these as only influencing the difficulty which the bacillus may have in passing from one individual to another. Changes undergone by the bacillus in the soil are not necessary to enable it to become pathogenic. It is evident that conditions of drainage may determine infection, but this is mechanical and not due to any properties in the soil itself. There may be infection of certain areas but the earth holds the bacillus in the same way as infected clothing might. The endemic character of the disease, especially in rural communities, may be largely due to local soil infection, and it has been shown that the bacilli may live for long periods in sewage-soaked earth. Filth and unsanitary conditions cannot originate typhoid bacilli. They must come from a previous source. Given their presence

it is evident that dirty conditions will render their distribution more likely, as water or food may be infected either directly or by flies. But filth can not be the only cause any more than typhoid fever can originate from a polluted water-supply which does not contain typhoid bacilli.

8. **Air.**—It is difficult to prove that infection is ever carried by the air, except with dust, and it may be regarded as of very rare occurrence. The view that the breathing of noxious gases may be a means by which the disease is conveyed is not proved.

The Organism.—The *Bacillus typhosus,* discovered by Eberth in 1880 and grown in pure culture by Gaffky in 1884, in a motile, flagellated bacillus, 1 to 3μ in length and .5 to .8μ in diameter. The ends are rounded and it sometimes occurs in chains. Under certain conditions it forms "pseudo-filaments." The size and morphology may vary with conditions of the culture media, age, etc. Flagella are often numerous. It does not form spores; the bodies seen at one or both ends of the bacillus and formerly regarded as spores are probably areas of degeneration. It is non-liquefying, non-aërogenic, aërobic and optionally anaërobic, growing best at 37° C. The toxin belongs to the intracellular group. It stains by the ordinary method and readily gives up color to a solvent. It grows readily in various media, especially in bouillon and milk, and on gelatine, agar, blood serum and potato. Motility is marked in certain media, especially bouillon. In the majority of instances it can be readily recognized in cultures. In certain cases it shows peculiarities and may be difficult to positively identify without careful investigation. Its determination is aided by the reaction to blood serum from an immune animal or from a human subject who has the disease.

The organisms are usually killed by a temperature of 60°. They are very resistant to cold and can live for three months in ice, while repeated freezing and thawing does not necessarily kill them. In distilled water they may live for three months but in ordinary water they usually disappear within from two to seven days. The duration of life in water is important, but it is not easy to say in any given water-supply how long the bacilli may live. This apparently varies with the amount of movement, light, chemical substances, etc., as well as the number of saprophytic bacteria present. The more contaminated the water, the shorter time do the typhoid bacilli live. They have been reported as living for eighty days in drinking water, but in reservoirs and dark wells they probably live much longer. In mud and the scrapings from wells they may exist for some weeks. They have been found in water-filters. In carbonated waters they can exist for weeks. In ordinary soils they seem to live for some months, and if bouillon be poured over the area they may live for a year, although in ordinary soil the bacillus usually disappears from the surface layers after a heavy rain. Under a leaking drain they have been found to live for two months. There is no evidence that they multiply in soil, but although the duration of life of the bacillus in various kinds of soil, as determined by different observers, varies somewhat, yet there is no doubt that they can live for some time. They may resist drying; thus, on cloth they have lived for nearly three months, while from cloth fouled by fæces containing the bacilli they have been recovered seventeen days later. On thread kept under suitable conditions they may live a year. They have been obtained from the dust of soil which

had been inoculated and then allowed to dry. The duration of life in fæces is variable, depending on many factors, especially on the chemical character and the other bacilli present, but probably as a rule it is short, although some writers state that they may live for months in cold weather.

The *B. typhosus* belongs to a group of organisms which are similar in certain particulars. Of these the colon, paracolon and paratyphoid bacillus, with the *B. enteritidis*, are the best known examples. They may be regarded as forming a series with the colon bacillus at one end and the typhoid bacillus at the other. Certain cultural differences are usually enough to distinguish them. In addition the agglutination reactions may be used. The intermediate group of organisms may be easy to distinguish from the colon or typhoid bacillus but may resemble each other closely. Buxton has suggested three groups: (1) the meat-poisoning organism, *B. enteritidis*, (2) psittacosis group, and (3) "typhoidal" group.

For many years, although the *B. typhosus* was constantly found in the bodies of those with the disease and could be grown in a specific manner, yet it had not been possible to reproduce the disease in animals. The bacilli and their toxins were pathogenic for mice, rats and rabbits, but the characteristic lesions were not produced. Recently Grünbaum has produced the disease in chimpanzees, 4 of which were infected; 2 died, and the others were killed on the twelfth and thirteenth days. Characteristic lesions were found, so that the possibility of producing the disease in animals can be regarded as proved.

There are many problems connected with the serum reaction which require solution. Thus there are patients who do not give the agglutination reaction at any time or only late in the attack. This may be true of mild or severe infections. It may be that some of these are due to different strains, and it has been advised that in such the reaction should be tried with different varieties or a mixed bouillon culture be used. It has been suggested that bodies which prevent agglutination may appear and that there may be disintegration products. This may be avoided by using very dense mixed bouillon cultures.

Bacteriology has, in the last few years, greatly increased our knowledge of the occurrence of the bacilli in the body. Certain of the abdominal viscera were regarded as the usual site of the bacilli. In 1885 the bacilli were isolated from the blood by Fraenkel and Simmonds, but this was regarded as an unusual occurrence. The increased number of observations which showed the bacilli in various parts of the body suggested that they must occur frequently in the circulating blood. Kühnau suggested that the bacilli were destroyed by the bactericidal action of the blood-serum in the culture media. By diluting the blood this was overcome, and the results proved the correctness of his views. By using large amounts of blood and diluting it, positive results are obtained in a large percentage of cases. They are found most frequently in the early stages of the disease. Coleman and Buxton have collected the records of 604 cases, in 75 per cent. of which the bacilli were obtained from the blood. Of 85 cases in the first week bacilli were obtained in 93 per cent.; of 198 in the second week, in 76 per cent.; of 115 in the third week, in 56 per cent.; and of 55 in the fourth week, in 33 per cent. Bacilli were found in the relapse in 18 out of 21 cases. They may be found in the blood at the time of post-typhoid chills. It may be considered that in all cases the bacilli are in the circulating blood at some

period and that this can be shown in nearly all patients by proper methods.

The bacilli are probably always present in the rose spots and have been obtained in a considerable number of cases in cultures or in sections of excised rose spots. As regards the viscera and glands it may be said that practically every one may be invaded. Abscesses in the skin, subcutaneous tissues, muscles or glands may all contain them. They have been found in the brain, cord and meninges. In a varying percentage of the complications in the glands they are present in pure culture; for example, in the parotid and thyroid glands, and also the breast, testicle, ovary and tubes. They may occur with suppuration or may be obtained by puncture without pus formation. In the lung they usually occur with other organisms but may be found in pure culture. Not infrequently they are found in the sputum. In the liver they are usually present and have been obtained in cultures from a liver abscess. In the spleen and mesenteric glands they are always present and may cause abscess formation. In the kidneys they are often present. In the circulatory system they are found in endocardial vegetations and in thrombi. They have been found in the sweat, but their occurrence in the urine is the most important. As a rule they are not found until late on in the disease, very rarely appearing until the third week, and in some patients they may not appear until convalescence. The frequency varies but probably about 25 per cent. is a fair estimate. The number which may be present is enormous and billions of bacilli may be excreted each day. In the stools the bacilli are comparatively few, but we are ignorant of the length of time during which they may be excreted, although cultures are generally negative in convalescence. The persistence in the gall-bladder is important, as here they may be present for many years, and it is possible that they may be passed into the intestines and out with the fæces. In certain parts of the body, such as the bones, they may be present for years in pure culture.

It must be considered that the bacilli may gain access to the body without the individual having had typhoid fever. This has occurred in the urinary bladder, the source of infection probably being a catheter. In the gall-bladder they have also been found without any history of an attack of typhoid fever. It has been suggested that some of the cases of epidemic jaundice are due to infection with the *B. typhosus*.

The typhoid bacillus may cause suppuration in many situations, but certain other organisms may be present with it and it may be difficult to say which is primary and which secondary. The colon bacillus, streptococci and staphylococci and others may be found, and these may be obtained from the blood during life. At autopsy it is common to obtain many organisms, among the most common being the colon bacillus, streptococci, staphylococci, *B. proteus*, *pyocyaneus*, *lactis aërogenes*, the gas bacillus and pneumococcus. In many of these the secondary infection is terminal or occurred after death.

At autopsy the *B. typhosus* has been obtained from almost every part of the body. The bacilli are found most constantly in the spleen, mesenteric glands and gall-bladder. In the alimentary tract they may be found in the mouth, especially in cultures from the tongue and tonsils, and some observers have reported them as being frequently found in the mucous membrane of the œsophagus. In the mucous membrane of the stomach, duodenum and

jejunum, ileum and cæcum, they are usually found, but in the colon the frequency depends somewhat on the distribution of the lesions, while in the rectum they are rare. They may be found in the lesions in various organs, as will be noted in discussing the symptoms.

Typhoid bacilli do not usually cause infection in animals, although Levy and Jacobsthal report having found typhoid bacilli in the pus from a large abscess in the spleen and a small abscess in the liver of a cow.

CHAPTER III.

THE PATHOLOGY OF TYPHOID FEVER.

By THOMAS McCRAE, M. D

External Appearance.—This varies greatly with the day of the disease on which death occurred. If early, as from severe toxæmia, the body is fairly well nourished and but little emaciated, while if late in the course there will be emaciation which may be extreme. The skin is usually very pale and there may be bed-sores. On section the muscles often show a characteristic change, having a curious, dry dark-red color. In some cases there may be extravasation of blood into the muscles and occasionally rupture. The microscopic appearance was especially studied by Zenker, who described the degeneration generally found. Abscess in the muscles is extremely rare. The bones and joints rarely show any change at autopsy.

The Nervous System.—When we consider the frequency and severity of the symptoms due to the nervous system the changes found after death are comparatively slight. Meningitis[1] is rare and the lesions may be one of two kinds—one in which they are not of suppurative character (the so-called serous meningitis), and second, the purulent meningitis. In the former group there are changes in the cerebrospinal fluid, with which changes in the meninges, consisting principally of œdema and hyperæmia with round-celled infiltration, may be associated. Typhoid bacilli are probably always present, and it may be that the action of their toxins is the cause of the changes in the meninges. In the purulent meningitis there is thickening of the meninges with a purulent exudate which is less on the surface than among the tissue-elements and between the meninges and the brain. The exudate contains many cells of various forms, especially mononuclears of all sizes, the large mononuclear phagocytic form predominating. In the arteries there are masses of cells which in places lift up the endothelium so as to block the lumen of the vessel. None of these changes can be regarded as peculiar to typhoid meningitis.

The brain shows no characteristic lesions. In some cases round-cell accumulations, especially in the perivascular spaces, have been described. Encephalitis and softening have occurred. Hemorrhage is exceedingly rare, while abscess is most likely to occur as a result of some secondary infection. Gross anatomical changes in the cord are rare. There have been cases in which with an acute spinal condition, such as myelitis, typhoid bacilli have been found in the affected area at autopsy.

The Respiratory Tract.—Erosions may be found in the mucous membrane of the nose and occasionally membranous deposits in the nose, on the soft palate and the tonsils.

The Larynx.—The mucous membrane very frequently shows catarrhal inflammation which has gone on to ulceration in a considerable number,

[1]The cases in this series have been studied by MacCallum and Cole. *The Johns Hopkins Hospital Reports*, vol. xii, 1904.

having been reported in as many as 26 per cent. of certain autopsy series. The ulceration may be superficial but often extends deeply and involves the cartilages. The majority of the ulcers are on the posterior part of the larynx, very often close to the insertion of the cords. They may also be found about the base of the epiglottis. With the involvement of the cartilages there may be marked necrosis and formation of extensive abscess cavities. Ulcers on the epiglottis are fairly common; they are usually superficial but occasionally cause considerable destruction. Œdema of the glottis is rather rare. The ulceration may be due to decubitus or there may be superficial erosions which become infected and extend. In others it is probable that there is involvement of the lymph follicles comparable to that seen elsewhere in the body, and typhoid bacilli have been found in these lesions both in sections and cultures. Changes in the cartilages are sometimes primary and not due to extension. Baer found ulcers in the larynx in nearly 20 per cent. of 1,109 cases.

The trachea and bronchi do not usually show any marked changes. The mucous membrane is often reddened and may show a few small erosions. Ulcers in the trachea are very rare, Baer finding 3 among 529 cases. No instance occurred in this series. The contents of the bronchi are usually scanty and principally viscid mucus.

The Lung.—Hypostatic pneumonia is comparatively rare and usually associated with cardiac weakness and a prolonged course. True lobar pneumonia is not especially rare. Horton-Smith reports it in 5 per cent. of his fatal cases and it was present in over 8 per cent. in the Munich statistics. It was found in 8 of 105 autopsies in this series. As a rule due to the pneumococcus, in certain cases the typhoid bacillus is the causal organism. In others a mixed infection has been present. Bronchopneumonia is common and was found in 34 of this series. Gangrene of the lung is not very rare and may follow a lobar pneumonia, especially in debilitated individuals, or occur as the result of an aspiration pneumonia. Ulceration in the larynx probably tends to favor the occurrence of gangrene. Abscess of the lung occurs more rarely and in some instances the causal organism is the typhoid bacillus. Hemorrhagic infarction is comparatively common; the source of the embolus may be in the right heart or the peripheral veins. Infarction due to a detached clot from a thrombus is very rare but occurred in two of this series. The infarct may be gradually absorbed or abscess or gangrene follow, with which an empyema is likely to be associated. In one case there were areas of embolic pneumonia due to emboli formed by masses of phagocytic cells derived from the mesenteric glands through the thoracic duct.

Pleurisy is rare, especially the serous form. It occurred in only 3 of the autopsy cases apart from pneumonia. Empyema is also rare, although reported in nearly 2 per cent. of the Munich series. It was present in only one of this series. The organism in both serous and purulent pleurisies may be the typhoid bacillus, while in others the pus cocci are present.

Acute or chronic tuberculosis may be found. In some of these cases cultures show mixed infection and complicated histological conditions.

Circulatory System.—The most important cardiac changes are in the myocardium. In the early stages the muscle shows comparatively little change, but later on some dilatation may be found and the muscle is flabby. This is by no means invariable, and the muscle may show but little change. On section it often has a curious yellow-brown (sometimes termed the dead-

leaf) color, and there may be quite marked mottling. In a recent case there were multiple abscesses in the heart muscle. Histologically there may be either interstitial inflammatory changes or marked parenchymatous degeneration. The muscle fibers may show marked vacuolation with considerable deposit of pigment about the nuclei. With marked interstitial change there may be abundant round-cell infiltration. Changes in the small arteries of the myocardium have been described as an inflammatory hyperplasia. Endocarditis is extremely rare. There were but 11 instances in the Munich series and only 3 cases in this one. The typhoid bacillus has been grown from the vegetations, but in others there has been secondary infection. Pericarditis is also, and was present on 1 of this series. It is sometimes secondary to pneumonia or a septic process.

The Arteries.—Involvement of the arteries, including the aorta, is more important and occurs more frequently than we have supposed. Fresh changes may be found in the intima of the aorta and coronary vessels. Thus, in 52 cases of this series, in which full notes were made on the condition of the aorta, changes were present in 30, which were apparently recent in at least 21. There may be extensive areas of yellowish sclerosis, showing on section an acute process, which it seems proper to regard as having arisen during the course of the typhoid infection. Of the coronary arteries of 62 cases, in which the condition was noted, there were 19 with definite sclerotic changes and in 4 others yellow areas in the intima were noted. In 13 of these cases the changes were early and could be interpreted only as of recent origin. The general character of these changes may be common to infectious processes generally and not peculiar to typhoid fever, but it is important that the condition of all the arteries should be carefully studied in future autopsies. In some there may be arteritis with possibly thrombus formation. Following the arterial thrombosis there may be gangrene. While this usually occurs in the legs there are some instances in the upper extremity and in the external carotid, with resulting gangrene of the ear and parotid gland.

The veins show changes more frequently than the arteries. Local thrombosis may be due to inflammatory change in the walls of the vein and in some cases is associated with the typhoid bacillus.

The Alimentary Tract.—Ulcers may be found in the pharynx (in 2.2 per cent. of Baer's 737 cases) but are more common in the œsophagus, as in 5 of this series. They were present in 4.5 per cent. of 223 cases collected by Baer. They may be part of the specific typhoid process or due to secondary infection. Œsophagitis was found in one case of this series. In patients dying some time after an attack, stricture of the œsophagus may be found. The stomach may show marked redness of the mucous membrane, and erosion or ulceration is not uncommon (2 per cent. of Baer's 1,108 cases). There may be doubt as to the specific nature of the ulceration found in the stomach, as ordinary gastric ulcer may co-exist with typhoid fever. Redness and swelling of the duodenum have been noted, but it is not proved that these lesions are specific. Seven cases of ulceration in the duodenum were reported by Louis and one by Andral.

Intestines;—On opening the abdominal cavity the intestines are frequently distended, this being usually most marked in the colon. The lower part of the ileum may be of normal size or even somewhat contracted. The peritoneum covering the bowel may show a large number of hemorrhages.

The areas on the outside of the intestine corresponding to the ulcers are deeply congested but show no granulation tissue formation as in a tuberculous ulcer and are often very soft in their central parts, sometimes losing the dark-red color and being rather grayish-green, depending on the depth of the ulcer. The usual changes which occur in the bowel are most easily described in the four classical stages.

1. *Hyperæmia and Hyperplasia.*—This involves the lymphoid tissue in the lower part of the jejunum, the ileum, and to a variable degree the appendix and the large intestine. The lymph follicles are swollen, grayish-white in color and may project for some distance. The solitary glands may also be greatly swollen and are sometimes very prominent. There is nothing absolutely characteristic of typhoid fever in this hyperplasia but it is rare to find such changes occurring with fever in any other disease in adults. In children it has been noted when death has occurred from other febrile conditions, and in early life it may be very difficult to decide as to the nature of intestinal lesions by the gross appearance.

Microscopic examination at this early stage shows a condition of marked hyperæmia. There is a great increase in the number of cells in the tissues, which may be so marked as to compress the smaller bloodvessels and give the grayish appearance so often seen on ordinary examination. The cells are of various kinds. There is always a large number of ordinary lymphoid cells and also larger epithelial cells; some of these are phagocytic in character and the swelling of the lymphoid tissue may be due almost entirely to their formation. A certain number may contain red corpuscles.

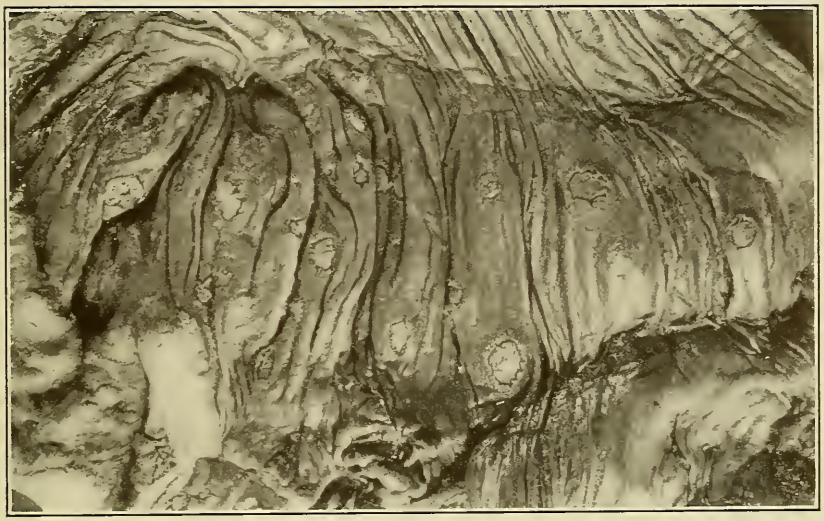
The number of areas which show hyperplasia varies greatly, for in some there may be only a very few infiltrated patches, while in others they may be so numerous that there is hardly an unaffected patch in the lower two-thirds of the ileum. As a rule the extent of the swelling is less in children than in adults. This process usually reaches its height from the eighth to the tenth day. Two modes of termination are possible, resolution or necrosis. The former is probably of much rarer occurrence than necrosis but it is very difficult to know how often resolution occurs. The process is one of absorption and offers no special peculiarity; fatty changes occur in the cells, which are then gradually absorbed. The patches which are undergoing absorption show at first a grayish-yellow color and then gradually collapse—at first in the centre and from this toward the periphery,—which often gives them a rather curious dotted or reticulated appearance. Much pigment is usually left, giving the "shaven beard" appearance. With this there may be a slight amount of necrosis giving rise to small areas of ulceration but these are small and superficial. It is possible that small hemorrhages may occur at this stage.

There is great variation in the extent of this process and in the co-existence of it with definite necrosis. We sometimes find the two side by side and with varying relative extent.

2. *Necrosis and Sloughing.*—This is probably due to several causes as the diminished blood supply from pressure on the vessels and the presence of thrombi, as well as the action of toxins. The degeneration of the phagocytic cells beneath the endothelium of the vessel probably influences the formation of thrombi. Mallory has described this process also in the spleen and mesenteric glands. The extent of necrosis varies greatly; it may be superficial and involve only the mucosa, or extend into the submucosa. As a rule

PLATE I

FIG. 1



Ulcers in the Colon.

FIG. 2

Swelling of Peyer's Patches, with Slight Ulceration.

PLATE II

FIG. 1

Ulcers Beginning to Heal, with a Perforation in the Centre of the Larger One.

FIG. 2

Healing Ulcers.

the process is most marked low down in the ileum, and in some cases practically the whole lumen of the bowel for some distance above the ileocæcal valve may be affected. In the colon, the extent of necrosis is very variable and in the solitary glands may involve only the most prominent part of a follicle. There may be every variation in the extent, number and depth of the areas of necrosis.

3. *Ulceration.*—With necrosis fully established, separation gradually occurs, usually beginning at the edges and extending inward. The process does not usually advance equally throughout the whole area, so that the slough is rarely thrown off in one piece but as a number of smaller portions. In large ulcers, areas of ulceration and some still covered by slough may be seen. The ulcer left after this process varies greatly in extent and in depth. Some may be very slight—from 3 mm. to 2 cm. in diameter. The smaller ones usually result from changes in the solitary follicles, while the larger ulcers are usually on the site of the Peyer's patches. Adjoining ulcers may coalesce so that almost the whole surface of the bowel forms one large ulcer, as is especially likely to occur at the lower end of the ileum with the ileocæcal valve involved in the process. The depth of the ulcers varies greatly. They may be superficial, with perhaps not the entire thickness of the mucosa involved, or the slough may extend down to the submucosa or the muscularis, which forms the floor of the ulcer in the majority of cases. In rare instances there may be extension of the ulcer after the separation of the slough, but in the majority the ulceration extends to its greatest depth with this. It is usually considered that perforation occurs most frequently at the time of separation of the slough, while secondary ulceration may explain its recurrence at later periods.

The shape of the ulcer is very variable. They are commonly more or less irregularly oval, but show all varieties of outlines. While the long axis is usually parallel to that of the intestine, in some cases the opposite occurs, and annular ulcers involving the whole circumference of the bowel have occurred. The edge of the ulcer is usually sharp, and for a time the margins may be quite steep in consequence of infiltration in the tissues about. The edges are usually soft, may be congested, and are sometimes undermined, although this is not common. The base of the ulcer, shortly after sloughing has occurred, shows a more or less dark-red appearance, and there may be small portions of the slough still adherent. Later the floor of the ulcer becomes comparatively clean and after a time shows a slate color. At this stage, when the lower ileum shows the characteristic ulcers, swollen and hyperæmic Peyer's patches without any sloughing may be seen higher up the intestine.

4. *Cicatrization.*—This probably requires varying periods of time in different patients. The process begins with the appearance of thin granulation tissue which covers the base of the ulcer. The mucosa gradually extends in and the epithelium forms over this. The glandular elements are apparently restored. After the process is completed the area is usually somewhat depressed and at first is of rather a lighter color than the surrounding tissue. Subsequently there is usually the deposit of a certain amount of pigment. It is a question whether the lymphoid tissue is destroyed permanently in the areas of ulceration. While the above is a general description, there may really be much variation in every point. While the ulceration in certain cases is confined to the ileum, yet in a considerable number the large intestine

is involved, and as a rule this is more marked in the cæcum than in the colon. In children the lesions are not likely to be as marked as in adults. This is especially true of the depth of the ulcers and has been given as a reason for the lesser frequency of hemorrhage and perforation in childhood.

There may be combinations found in different parts of the intestine; healed and fresh ulcers may be found close together. With marked ulceration in the ileum the follicles in the colon may be swollen and show hemorrhagic areas without ulceration, or perhaps there is only one small ulcer in the large bowel, or many minute areas of ulceration. Very rarely is ulceration found in the large bowel alone. The appendix also shows much variation. Its mucous membrane may show no gross change, or there may be hemorrhagic areas or perhaps swelling with little ulceration. The colon may show a diphtheroid membrane over its surface.

Among the 105 autopsies of this series, in 4 there were no intestinal lesions; the site of ulceration in the others was: ileum 99, colon 59, appendix 15 (in 8 others the follicles were swollen but did not show ulceration), rectum 12, and cæcum (with the rest of the large bowel free), 5. In 2 ulceration occurred only in the colon, in one the small intestine being perfectly free, in the other showing some injection. The figures collected by Baer showed the site of ulceration as follows: jejunum, 5.9 per cent. of 1,358 cases; ileum, 89 per cent. of 1,423 cases; Meckel's diverticulum, 1.1 per cent. of 89 cases; some part of the small bowel, 97.5 per cent. of 623 cases; the ileocæcal valve, 6.7 per cent. of 89 cases; the appendix, 2.5 per cent. of 441 cases; the cæcum, 30.3 per cent. of 1,396 cases; the ascending colon, 10.3 per cent., transverse colon, 4.5 per cent., and descending colon, 2.6 per cent. of 621 cases; colon (site not specified), 29.1 per cent. of 1,181 cases; sigmoid, 6.9 per cent. of 101 cases; and the rectum, 2.4 per cent. of 1,056 cases. Baer collected 5 instances in which the colon alone was involved.

Hemorrhage.—If hemorrhage has occurred to any extent the bowel usually contains large amounts of blood. If the bleeding has been from a large vessel this may be found in an ulcer with a large slough. It is sometimes possible to find the vessel from which the bleeding occurred. If the hemorrhage has been from capillaries or small vessels the areas may often be found infiltrated with blood. In some ulcers the bleeding seems to have been at the edges.

Perforation.—The incidence of this may vary greatly in different epidemics and in different localities. Perforation was found in 30 of 105 autopsies in this series. It shows great variation in the time and situation, occurring more often in ulcers with adherent sloughs than in those which are clean. Perforation is in the lower part of the ileum in the majority; in only 5 of 32 cases with perforation in the ileum was the opening more than eighteen inches from the valve. The perforation may be in the appendix, as in 3 of this series, or in the large bowel as in 4. The sigmoid flexure is comparatively often the site of perforation in the large bowel. In some cases perforation may occur in the rectum, and if this is low down an abscess may form in the perirectal tissues. There are some recorded cases of perforation in a Meckel's diverticulum or in the jejunum.

Of the actual conditions which favor perforation we know little. When one examines the bowel with ulceration extending almost to the peritoneum the wonder is, not that perforation occurs, but that any escape. Violent muscular movements may be a cause, but of the influence of peristalsis it is

not possible to speak. Distension of the bowel may increase the chances of perforation but it is not possible to quote any figures which support this, or to say what is the relative influence of ulceration and other factors.

After perforation general peritonitis usually follows. There is much variation in the amount of fluid in the abdominal cavity but as a rule it is considerable. Adhesions may keep the process localized and abscess results, the perforation being closed by the omentum or by adhesions. Peritonitis without perforation and without any other evident etiological factor may occur, as in a case reported recently by Watson (*Lancet*, May 6, 1903), in which a boy, aged nine years, was admitted with general peritonitis. At operation the abdomen was found full of pus, death followed and at autopsy there was a general peritonitis; early typhoid ulcers were found in the ileum, but there was no perforation and no ulcer nearly through the bowel. In one case of this series at operation no cause for an early peritonitis could be found and cultures were negative. It is difficult to give an explanation of such cases. Peritonitis may occur from perforation of the gall-bladder due to the processes of the disease or from rupture of a suppurating mesenteric gland. There may be the accidental association of other conditions, such as an ordinary appendicitis, rupture of a gastric ulcer, or in women an extension from pelvic suppuration.

The Mesenteric Glands.—These stand in close relationship to the intestines and almost invariably show some involvement. In the early stages there is hyperæmia and infiltration, with swelling of the glands. This probably begins about the same time as the infiltration of the lymphatic structures of the intestines. Their size varies very much, being often as large as a walnut and rarely the size of a small hen's egg. Areas of necrosis may be found, and as a rule the glands are soft and on section almost diffluent. Suppuration may occur with the formation of an abscess which may rupture into the peritoneum. Usually the glands about the lower end of the ileum are especially involved, but those higher up in the abdomen may also show changes. The retroperitoneal glands are often swollen and even the glands in the thorax and in the neck may be involved. Involution probably proceeds equally with the process in the intestine and the glands gradually return to their normal size.

The Spleen.—The changes in this organ may be compared to those which occur in the lymphoid tissue of the intestine and in the mesenteric glands. The spleen is nearly always swollen at the beginning and during the course of the disease; the enlargement is usually moderate and the size is perhaps on an average about three times that of the normal organ. Very great enlargement of the spleen is not often seen. In 11 of this series the weight was over 600 grams, the greatest weight being 900 grams and the average 356 grams. The spleen is usually soft and may be almost liquid, so that it is difficult to make a section of it. In many cases it is very dark red and bloody on section. In 27 cases there were adhesions found, only 2 of these apparently being recent. Even fairly firm old adhesions do not necessarily prevent considerable enlargement. During defervescence the spleen diminishes rapidly in size. The capsule becomes relaxed and wrinkled, and owing to the hyperplasia the organ becomes tougher than normal. Rarer conditions, such as infarction and abscess, may occur, but these were rare in this series, infarct being found in only one case. Either an infarct or an abscess may rupture into the abdominal cavity and cause peritonitis.

Rupture of the spleen has occurred and may happen spontaneously or as the result of injury.

The histological changes are associated especially with the presence of the typhoid bacilli, which can usually be obtained in cultures at autopsy. They are found in the spleen in irregularly arranged groups. Sections made in the early stage of the disease show very marked hyperæmia, with overdistension of the blood channels. Later on there is marked hyperplasia both of the splenic cells and of the stroma, and with this there are usually large numbers of phagocytic cells found. Focal necroses are constant and abundant.

The Liver and Bile Passages.—The liver early in the disease is usually hyperæmic, firm and somewhat enlarged, but later it becomes paler and more friable. The structure of the lobules is usually not so evident on section. The most marked change is a parenchymatous degeneration, which may vary much in different parts. The liver cells at first are granular, turbid and show fatty change, while after this they may contain granules and drops of fat and later on disintegrate. This process begins most commonly at the periphery of the lobule and is usually more marked here than at the centre. There may also be nodular areas which have attracted more attention. There probably are two kinds, one being considered as lymphoid nodules, while the others are apparently necrotic. Mallory considers that there are two varieties of these lesions; in one there are phagocytic cells in the lymph spaces and around the portal vessels, which are probably due to the action of toxins. The second variety is due to the obstruction of the capillaries by phagocytic cells which have been carried by the portal circulation from their point of origin from the endothelium of the vessels of the intestine and spleen. Following this the liver cells lying between the capillaries undergo necrosis. No definite connection has been proved between the typhoid bacillus and these areas, and it is not considered that these lesions are necessarily peculiar to typhoid fever as they may occur in other acute infections.

Abscess of the liver is extremely rare, there having been only 2 in this clinical series and 1 in the autopsy records. The typhoid bacillus is the causal organism in a small number but in others the pus organisms are present. Acute yellow atrophy has been noted in connection with typhoid fever. Pylephlebitis is rare and is usually secondary to some condition in the peritoneum or mesenteric glands.

The changes in the gall bladder and bile passages are very important. Acute typhoidal cholecystitis with intense inflammatory reaction occurred in one of this series. Ulcers in the gall bladder offer no special peculiarities and may cause perforation just as in the intestine. Ulceration in the common bile duct is apparently very rare. There can be no question of the influence of typhoid bacilli in the gall bladder in favoring the subsequent formation of gall stones. Great importance has been attached by some writers to the possibility of relapses being often due to reinfection from the gall bladder, but this has not been proved.

The Pancreas.—Changes in this organ are usually not regarded as of importance. In the early stages of the disease the gland is enlarged and deep red in color. Histologically, dilatation of the vessels is found, with serous infiltration of the parenchyma. Later on the gland apparently returns to a normal condition.

The Urinary Tract.—The kidneys show much the same changes as the liver and spleen, that is, they are slightly enlarged, with a color redder than normal and hyperæmic on section. As the disease progresses the kidney may enlarge still further and have a yellowish tint. Subsequently after a long attack the kidneys may become smaller just as the liver does. The histological changes are cloudy swelling with granular degeneration; this is usually seen first in the cortex and only later, and usually to a less degree, in the medulla. In certain cases there may be a definite acute nephritis, which was found at autopsy in 8 of this series. It is generally that of an acute parenchymatous, hemorrhagic type, with the changes more marked in the parenchyma than in the interstitial tissue. Numerous small areas, infiltrated with round cells, which may pass on to suppuration, causing the so-called miliary abscess, have been described. These are probably usually due to micrococci but in some instances typhoid bacilli may be isolated from them. Lymphomatous nodules similar to those which occur in the liver have been noted, and some observers say that they occur about half as frequently as in the liver. Multiple abscesses in the kidneys were found in 7 cases of this series. In the pelvis of the kidney and in the ureters small hemorrhages may be seen. Pyelitis is very rare and was found in only one case. Diphtheritic inflammation of the pelvis of the kidney may occur.

The bladder often shows hemorrhage into the mucous membrane. Catarrhal states occur not uncommonly and there may be also diphtheritic inflammation, which may cause a phlegmon. The occurrence of cystitis is not very common and only 4 were found at autopsy in this series. Abscess of the prostate is rare and was found in one of the series.

In considering the histological changes, an important point is the absence of typical inflammatory lesions, except such as cholecystitis and meningitis. Special attention has been given to this subject by Mallory, whose conclusions may be summarized. The typhoid bacillus produces a mild toxin which causes proliferation of endothelial cells, epitheloid in character. These are produced (1) along the line of absorption from the intestine both in the lymphatics and bloodvessels, (2) through the general circulation, especially where the circulation is slowest and (3) throughout the body in the lymphatics by absorption of the toxin eliminated from the bloodvessels. These cells increase both in number and size and show marked phagocytic properties especially toward the lymphoid cells. This occurs especially in the lymph nodes and along the lymphatic vessels. This process is proliferative and may represent the extent of change in the solitary follicles in mild attacks. It may however extend further, disintegration of the phagocytic cells with fibrin formation, forming thrombi which block the lymphatic vessels. In the veins similar accumulations occur beneath the endothelium, probably in lymph spaces. By these and the resulting fibrin formation the vessels are occluded, and as the blood supply is interfered with, necrosis results. The arteries are not affected by this process. Following the necrosis, inflammatory exudation occurs in which polymorphonuclear leukocytes are rarely found.

The changes in the mesenteric lymph nodes and spleen do not differ greatly, the increase in size being due to the proliferation of the phagocytic cells. In the liver, two varieties of focal lesions are found, one in the connective tissue around the portal vessels and therefore outside the lobule, the other in the lobule among the liver cells. The former consists of an increase

of lymphoid and plasma cells, with the large cells derived from proliferation from endothelial cells. The lesions occurring in the lobule itself are due to the collection of cells from two sources, some being derived from the living endothelium of the liver capillaries but the majority being carried by the blood current from the intestine and spleen. When a capillary becomes blocked by these large cells there is a process much like that found in the intestine, and other cells are added both by interference with the circulation and by division. The liver cells in these areas undergo necrosis and fibrin appears between the cells. These areas do not show any signs of marked invasion by polymorphonuclear leukocytes.

These large phagocytic cells may pass into the general circulation and cause focal lesions in the kidneys by occlusion of the veins of the pyramids. Similar changes may be found in the heart and testicle. The formation of thrombi, especially in the veins, may be due to a similar condition. The bone-marrow, which has been specially studied by Longcope, shows a condition much like that described in the intestine lymph nodes and spleen. There is congestion and œdema, with areas of necrosis and the presence of the large phagocytic cells. The blood-forming cells show general hyperplasia with a marked relative increase of the lymphoid over the granular cells. The myelocytes are decreased, agreeing with the diminished number of polymorphonuclears in the blood, and intercurrent infections do not alter this greatly. The eosinophiles are greatly diminished in number. In cases where some complication, such as general peritonitis, was present, the blood-forming cells show marked degeneration. There is some question as to the mode of origin of the large phagocytic cells. It has not been settled whether they are exudative or derived entirely from the fixed connective tissue cells.

Mode of Infection.—The explanation of the exact mode of infection is still in doubt. Entrance by the tonsils has been suggested, which would make the infection primarily by way of the lymphatics and blood. Do the typhoid bacilli gain entrance to the body through a perfectly sound mucous membrane, or is a local lesion necessary? It may be that the absorption of toxin first causes changes in the intestine and that the typhoid bacilli gain entrance later. The instances of infection without intestinal lesions suggest that the bacilli may enter through a sound mucous membrane, but it is possible that minute lesions are not observed or have healed before the opportunity for examination. The finding of typhoid bacilli in the stools of apparently healthy individuals, and the fact that, of the total number of persons exposed to infection by the ingestion of typhoid bacilli, in only a certain number does the disease develop, suggest that local conditions in the bowel may have an important influence. But there are so many possible factors that it is not safe to draw any positive conclusions.

Types of Infection.—Infection with the typhoid bacillus may be followed by different results, in one the typical disease, in another a local lesion, again a general infection without local lesions, or the brunt of the attack may fall on one organ. In some instances typhoid bacilli may be present in the stools without any clinical evidence of disease. It has not been proved that there is any relationship between the severity of the disease and the number of bacilli found in the blood. A patient may have a severe infection and yet the blood cultures be absolutely negative. Again, it has been noted that the severity of the attack does not necessarily agree with the virulence of the bacillus. Thus in the epidemic at Trier, virulent cultures were obtained

from patients with mild attacks, and *vice versa*. It has been pointed out that we must distinguish between the toxicity of the bacillus and its invasive capacity. The passage through animals probably diminishes the former but increases the latter. This goes to explain the fact that in many epidemics the invasive properties were marked but the toxic properties became weaker, which would account for the comparatively low death-rate in the Spanish-American War.

The forms of infection may be classed as follows:

1. **With the Usual Intestinal Lesions.**—This is the commonest form and includes the majority of cases.

2. **With Slight or Atypical Intestinal Lesions.**—This group is of uncertain frequency. Slight lesions in the bowel may be difficult to find and may be absent in the ileum but present in the colon or stomach The lesions may have been without necrosis and entirely healed before death. The diagnosis may be made during life or at autopsy by bacteriological findings.

3. **Cases without Intestinal Lesions.**—There were 4 such cases in the present series. There seems no question of their occurrence, although it may be difficult to say that slight lesions have not healed. The diagnosis can be made positively only by obtaining the bacilli during life or at autopsy.

4. **Local Infection.**—This has occurred in the urinary bladder and some cases suggest that it may also occur in the gall bladder. There is always the possibility of a mild unrecognized previous general infection.

5. **Terminal Infections.**—The typhoid bacillus has not usually been regarded as one which might cause a terminal infection, as for example in a patient with malignant disease, but in this series there have been two such instances. There seems no reason why the typhoid bacillus should not cause a terminal infection in the same way as other organisms. Both of these were patients with malignant disease and both were without intestinal lesions. Typhoid bacilli were obtained from the blood during life.

6. "**Paratyphoid Infections.**"—It seems justifiable to include the various infections caused by organisms which, while closely related to the *B. typhosus*, are still distinct, under the general heading of typhoid fever. There were 8 of these in the last 500 cases of this series.

7. **Mixed Infections.**—In a certain number of cases, in addition to infection with the typhoid bacillus, another organism is added. This may be the colon bacillus, pneumococcus, streptococcus or staphylococcus. This may be early in the attack and coincident or occur as a secondary infection which is frequently a terminal one. In the latter the condition of the body, due primarily to the typhoid infection, gives opportunity for the development of other organisms.

CHAPTER IV.

THE SYMPTOMS OF TYPHOID FEVER.

By THOMAS McCRAE, M. D.

"There is no disease, in fact, which exhibits a more protean character, from predominence of certain symptoms, and from the presence of complications."—MURCHISON.

Introduction—The manifestations have an almost infinite variety; from the onset, throughout the course, in the termination and sequelæ we may expect anything. Not only is there great difference in the symptoms shown by different patients but the character of the disease in the same locality may vary greatly from year to year. Thus in one year the patients may have few rose spots while in the next the rash as a rule is very profuse, and the same may be seen in the occurrence of hemorrhage. This may be due to the character of the infecting organism. For the student it is most essential to realize that the classical description of the disease does not fit every patient and this makes it so important that the disease should be studied from the patient and not from text-books alone. No symptom or sign is necessarily present, a point never learned by some men who refuse to make the diagnosis of typhoid fever unless certain classical features are found.

INCUBATION.

The period of incubation may be impossible to determine exactly and it probably has limits varying from three to twenty-three days. In the instances reported by Dufloeq and Voisin, in which the patient swallowed a virulent culture of bacilli with suicidal intent, there was headache and malaise on the third day, fever on the fourth, epistaxis and rose spots on the eighth and a palpable spleen on the ninth day. The report of the Spanish-American War Commission gives the average period of incubation, based on a study of 780 cases, as ten and one-half days, the shortest being slightly less than six days. The first symptoms are often so indefinite that no positive statement can be made as to the incubation period. At first the patient may feel out of sorts, be easily tired and complain of general malaise without anything more. Probably the majority of patients have some symptoms during the period of incubation.

The Onset.—This may be very variable. The most frequent symptoms at onset in this series were as follows: headache 1,117, anorexia 825, diarrhœa 516, abdominal pain 443, general malaise 436, vomiting 404, cough 393, chilly sensations 392, chill 334, epistaxis 323, fever 285, nausea 255, constipation 249, backache 215, sweating 207, general pains 196, weakness 112, delirium 65, dizziness 61, stiffness of the neck 47, sore throat 32, herpes 18, deafness 13, insomnia 11, photophobia 6, intestinal hemorrhage 4, convulsions

3, arthritis 3, syncope 3, jaundice 2, retention of urine 1, otitis media 1, hiccough 1 and bone lesions 1.

The most common features at onset are headache and anorexia. The headache is frequently severe and is often referred to the top of the head, while in others it is only a more or less general soreness. After these in frequency come diarrhœa and abdominal pain. To the former much importance is given in the usual descriptions but it must be kept in mind that in many patients it has followed the taking of a purgative. The less frequently purges are given early in the disease, the smaller will be the number of cases of diarrhœa. The occurrence of abdominal pain in nearly 30 per cent. is surprising and also important as this may lead to error. Nausea and vomiting occurred in a large number when we think how rare these are during the course of the disease.

Of the general symptoms malaise was the most common, being found in 436. Chills and chilly sensations are comparatively common. The percentage with chills at the onset (22 per cent.) is high, especially as many writers consider that they are rare. This being a malarial district careful inquiry is made for a history of chills but this is not accepted unless there is a positive history of "shaking." We have to be careful not to accept the "dumb chill"—common in this locality—as the true variety. General pains, backache, weakness and dizziness occur in a certain number. Fever is not a common complaint of onset when we remember that it must be almost always present; sweating may be associated with it, although usually the skin is dry. The classical epistaxis was present in 325 or a little over 20 per cent. From the importance placed on it by the older writers one wonders if epistaxis has not become less frequent. Herpes was comparatively rare and was found in 18 of the series or 1.2 per cent.; its infrequency is an important point to keep in mind in the diagnosis of doubtful cases. Atypical rashes have been reported but are not common.

The conditions which occurred rarely are of special interest as showing possibilities. Hemorrhage from the intestine may be the first symptom but this is, of course, not at the time of onset of the disease, although we use the term to mean the first symptom noted by the patient. In the case of the patient whose first symptom was a bone lesion, it is possible that typhoid bacilli may have set up the local changes in the bone at the same time as the general infection was progressing. In speaking of the onset it must be remembered that the first symptoms appreciated by the patient and the real beginning of the disease may be widely apart.

Special Modes of Onset.—While in the majority of cases the onset is slow and insidious yet it may be more or less sudden and with unusual features. In a certain number the onset is quite sudden, a point to which Manges has directed attention. The beginning may be with the ordinary symptoms in a very acute form or with marked symptoms in one system, so that the patient can give the exact time of onset. The most common of these methods of onset are as follows:

1. **With Marked Nervous Manifestations.**—These are very various. The onset may be with convulsions as in 3 of the series. This is especially likely in children but may also occur in adults, as in one patient who, after working all day, had gone to bed feeling perfectly well. His room-mate waked in the night and found the patient having repeated convulsions, which continued at intervals until the next day. There was no history of epilepsy,

alcoholism or exposure to lead. In some instances there may be marked delirium or stupor at the onset. Occasionally there is severe acute mania and patients have been committed to an asylum. The disease may begin with symptoms which suggest meningitis, such as severe headache, delirium, retraction of the head, etc. Many of the symptoms of meningitis may be present without any organic changes in the membranes and in such the diagnosis may be made with great difficulty, although lumbar puncture is of much assistance. The early headache may be very severe and if it be of a neuralgic type the diagnosis may be difficult. In some of these cases the attack is suggestive of influenza.

2. **With Marked Pulmonary Symptoms.**—There are instances of acute laryngitis at the onset but perhaps the most common condition is to find the initial bronchitis so severe that it quite overshadows the other features. This has often a very suggestive character, the cough may seem loose but there is little sputum. Again the onset may be with an ordinary acute lobar pneumonia, the "pneumotyphoid" of the French. This has all the usual features and there may not be a suspicion that we are dealing with anything more than an acute lobar pneumonia. In some instances the temperature may fall about the seventh day but soon rises again. The organism is usually the pneumococcus and very rarely the typhoid bacillus. It is well to recognize frankly that this mode of onset may completely mislead the physician.

There is another lung condition sometimes found at onset which is difficult to diagnose definitely, as atypical signs and course are the most marked features. There is usually some distress and an increase in the respiration rate but the ordinary features of pneumonia are lacking. There is generally diminished expansion on the affected side, vocal fremitus is normal, possibly slightly increased or perhaps even lessened somewhat, there is moderate dulness and on auscultation either suppression of the breath sounds or distant tubular breathing. In some cases the diagnosis of pleurisy has to be considered but the subsequent course and the negative results of punctures suggest that it is a "low variety" of pneumonia. In some, a small patch of distinct tubular breathing can be made out later on. The duration is indefinite, in some only a few days, in others lasting perhaps two weeks; it usually clears up slowly. This condition seems more frequent on the right than on the left side. It may give great difficulty in diagnosis if there be no positive signs of typhoid fever. Pleurisy at onset may also cause confusion. In a patient recently under observation the onset was sudden with high fever and a friction rub which disappeared with the appearance of an effusion on the third day. In this series pleurisy at onset has been rare.

In some patients the pulmonary symptoms may suggest tuberculosis. This is most likely if the patient has been feeling badly for some time and there are indefinite signs in the lungs. The possibility of the two diseases existing in the same patient has to be kept in mind.

3. **With Marked Gastro-intestinal Symptoms.**—Tonsillitis has been noted early in the attack but is rare. The onset may be with severe vomiting and marked abdominal pain so that some form of poisoning is suggested, but the vomiting usually does not persist. In others the diarrhœa may be so severe as to suggest an acute enteritis, especially if the stools have a watery character. In some the onset may be with gastric and intestinal disturbance accompanied by slight fever. The temperature may fall and the attack be

regarded as of no importance, only the subsequent fever showing the real condition.

A deceptive method of onset is that with severe abdominal pain, as this leads to the diagnosis of an acute abdominal condition and it is by no means rare for such patients to be explored. The pain may be especially in the right iliac fossa with marked tenderness. If this has been of rather sudden onset the diagnosis of appendicitis may easily be made. If the pain be in the upper abdomen, cholecystitis or some acute gastric condition may be suspected. An important point in the recognition is the fact that the abdominal pain of typhoid fever—except that due to complications—is much relieved by hot applications. The use of these and careful watching will, as a rule, prevent error or at any rate a needless exploration. Too much emphasis cannot be laid on the possibility of mistaking the abdominal pain which occurs early in typhoid fever for that due to appendicitis. The combination of pain, tenderness, rigidity and muscle spasm is not found in typhoid fever apart from complications.

4. **Onset with Renal Symptoms.**—In rare cases there may be the features of acute nephritis—the "nephrotyphoid"; the urine may be scanty and contain albumin, tube casts and blood. These have been very rare in this series. Retention of urine is quite common at the onset and should always rouse suspicion of typhoid fever in a doubtful febrile condition.

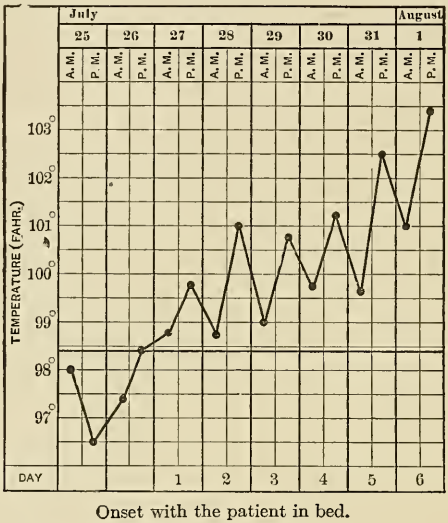
5. **Onset with Complications.**—In some instances there may be no suspicion of any illness, the patient only complaining of slight symptoms, until hemorrhage or perforation occurs. Four patients of this series were admitted with general peritonitis subsequent to perforation of a typhoid ulcer, without any history of illness before the onset of the severe abdominal symptoms. In such patients it is only when the abdomen is opened that the condition may be recognized unless there happens to be a marked crop of rose spots. If by any chance the agglutination reaction is tried this may give the diagnosis.

6. **The Ambulatory Form of Onset.**—Under this term two different types of cases are described. Some writers use it to designate very mild attacks which are not severe enough to compel the patient to go to bed. As a rule, however, it is applied to the group composed of those who keep about and may be at work having more or less fever. These are likely to have severe attacks and in hospital practice are well recognized as swelling the mortality. They supply a number of the instances in which the apparent onset is with marked nervous features.

The day of onset of the disease may be difficult to determine. As a rule it may be considered as the day on which the patient gives up work or goes to bed. This is not always exact as there may be no question that the patient was ill for some days before he went to bed. In women or children there is often a history of their having to lie down for part of the day. This may be considered as part of the attack. Men frequently give up work for a day or two and then return to it until compelled to give up again. A striking feature is the change which may occur in the patient's condition after he has been put to bed, which is especially marked if he has been fighting the disease. A patient who has walked into the hospital may be almost unable to lift his head in two or three days! The temperature of the patient who has been at work or going about may not be high but after a few hours rest it rises rapidly. In hospitals, normal or even subnormal

temperature records on admission are seen especially in patients who have walked some distance or had a long wait before admission. In such there may be a rise of four or six degrees within a few hours after they are put to bed.

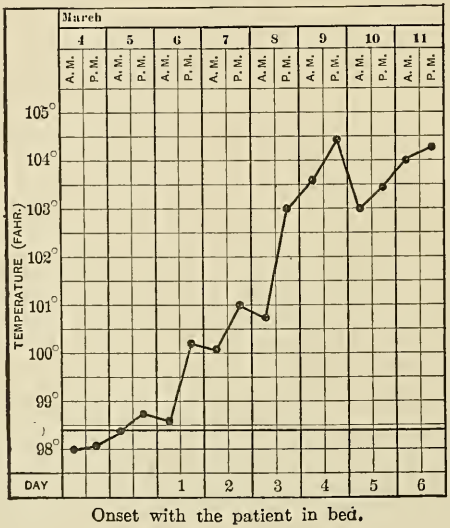
FIG. 1.



Onset with the patient in bed.

The character of the early fever curve is of interest. While the step-like rise so often described (Fig. 1), is not uncommon yet in many instances the fever may attain a maximum by the third or fourth day. This is well shown in patients who for some reason have been in bed at the time of onset (Fig. 2). In the onset with marked symptoms in one organ the temperature

FIG. 2.



Onset with the patient in bed.

may rise rapidly. The same may be observed in the onset of a relapse. This may be by a gradual increase in the temperature each day or it may rise suddenly from normal to 103° to 104° F.

As a rule by about the end of the first week the evening temperature reaches 102° to 104° F., by which time the appearance is often distinctive. The face is somewhat flushed, has an anxious look, and the eyes are bright. There is rarely any delirium at this stage but the patient may be easily confused and a certain mental slowness is frequently observed. This is especially noted when the history is being taken, the patient often having difficulty in remembering occurrences exactly and may have special trouble in giving times and dates. Some may show a little more confusion toward evening or at night. The tongue is very often coated and white; the breath is frequently foul. The abdomen is sometimes distended and there may be slight gurgling and tenderness in the lower right quadrant. The bowels are often constipated, although there may be diarrhœa early in the course, especially if purgatives have been taken. Bronchitis is common, often accompanied by a hacking cough but with little expectoration. The pulse rate is usually low in proportion to the fever; thus a patient coming in with a temperature of 104° may have a pulse between 80 and 90. It is often full in volume, may be dicrotic, and the blood pressure is usually about normal. The spleen may be felt very early. The rose spots are rarely made out until the end of the first week.

FEATURES OF THE COURSE.

In the second week of an ordinary attack the symptoms usually become more severe; the fever is higher, generally remaining fairly constant, and there is very little remission either in the morning or after sponging or baths. The mental condition as a rule is dull and they will often lie quiet, paying little attention to what is going on about them and dozing most of the time. They can usually be aroused and will answer questions apparently perfectly correctly, but, to any one who knows the circumstances, quite incorrectly. One curious disturbance is the loss of definite ideas of time. It is important to remember this, because a patient who is apparently perfectly rational may state that he has received no nourishment for twenty-four hours, when perhaps not as many minutes have elapsed since his last feeding. Nurses are often subjected to unfair criticisms on account of these statements and their unreliability should be kept in mind. In such cases it is well to explain the matter to the friends. The facial appearance usually changes during the second week, the early flush disappears and they have a heavy, dull look. The lips are dry, the tongue is coated and in severe cases is heavily furred. The breath is foul. There may be sordes on the lips and teeth if the attack be a severe one. The abdominal symptoms usually become more marked, there is a greater tendency to distention, and diarrhœa may appear or become aggravated. At this time or later there may be some complaint of abdominal pain. As a rule the bronchitis has subsided. The pulse usually becomes more rapid, probably is dicrotic, shows the soft quality so often present in typhoid fever, and the blood pressure may fall slightly.

Death may occur during this week, usually toward the end, and generally from profound toxæmia, although both hemorrhage and perforation may

occur. In mild attacks the temperature may have begun to fall and be about normal at the end of this week.

In the third week the conditions of the second week may be aggravated or there may be signs of the attack coming to an end. If it be a severe one the emaciation now becomes noticeable, the weakness is more marked and the whole appearance of the patient is changed. The mental condition may continue dull; there may be a muttering delirium and muscular tremor in the severer cases. The tongue is often dry, tremulous and protruded with difficulty; it may be swollen, fissured and heavily furred. The abdominal symptoms may be more marked and diarrhœa or distension appear for the first time. The pulse rate usually increases, varying perhaps from 120 to 140 in severe cases. The heart sounds usually show changes, the first very often becomes feeble and indefinite and may almost disappear at the apex; the second is very often short and sharp. In others there may be embryocardia. The pulse is usually small, very soft, and the blood pressure low, averaging perhaps 100 mm. Hg. Lung complications may occur, either ordinary lobar pneumonia or a hypostatic condition. Distension, hemorrhage and perforation may occur. The back may show signs of irritation and bed-sores appear.

If the attack be of a milder type, toward the end of this week the temperature begins to come down, both the morning remissions and those after the baths being more marked. The mental condition improves, the tongue cleans and all the symptoms show improvement. The wasting usually ceases. It is at this time that the friends are so apt to ask about the expected crisis on the twenty-first day, an idea which has probably risen from the fact that in the majority of patients improvement begins about the end of the third week.

In the fourth week in the ordinary attack convalescence begins. The temperature gradually declines, the whole condition improves, and the appetite returns. In many cases, however, while the temperature comes down it does not reach normal and may remain about 100° F. in a very provoking way. In severe cases the condition may be an aggravated repetition of that in the third week. The mental state is worse, the patient lies oblivious to his surroundings and perhaps in a muttering delirium. There may be much muscular tremor and subsultus tendinum. In this condition involuntary passage of the urine and fæces or retention of urine are common. The pulse usually becomes more rapid, reaching perhaps 140; it is small and the blood pressure may be lower than before. The abdomen is often distended and there may be diarrhœa. In such a condition there is often great difficulty in making the patient take sufficient nourishment and water. During this time there is always danger of pulmonary complications, and hypostatic pneumonia may occur. Bed-sores have to be especially guarded against. In the following weeks severe cases may still show continued fever with all the features spoken of in the fourth week, but as a rule there are signs that the attack is drawing to a close. The fever becomes more irregular, although it may come down to perhaps 100° or 101° F. and then remain persistently about the same figure. At this time relapses and recrudescences may occur and the patients are subject to some of the latter complications.

Attacks of collapse may occur with a sudden drop of temperature, even to subnormal, and signs of severe shock. There is cyanosis, the respirations are shallow and rapid, the pulse is small and there may be vomiting and

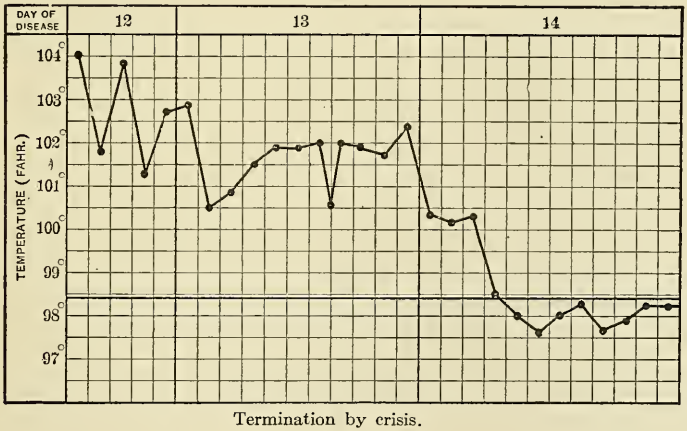
diarrhœa. The abdomen is negative. The patient may die or gradually improve. It may not be possible to give any explanation of the condition

While general descriptions may be given, there is no account that can fit all cases. The general features may be mild and severe complications appear or toxæmia may be marked and continue with high fever but no other special features are present. The early part of the attack may be mild and the temperature show signs of coming down when suddenly all the symptoms become worse and the patient passes into a serious state. In others the temperature may have come down but the toxæmia and prostration continue. Every possible combination may be present.

General Appearance.—The aspect early in the disease is frequently very characteristic. The face may be somewhat flushed and the eyes bright but with this there is a curious dull appearance more easily recognized than described and which in certain cases makes one suspicious of the diagnosis. The patients will often go into a doze during the examination and usually pay little attention to what is going on around them. In the beginning of the second week the expression usually becomes duller and toward its end the patients lie with a listless heavy look. There are, however, patients of an acute nervous type who are very alert and whose senses, especially hearing, seem keener than normal. Toward the latter end of the disease the color usually leaves the face and they have often a pale, sallow look which is not necessarily associated with anæmia. During convalescence the appearance is often characteristic if the attack has been at all severe as the marked emaciation, associated with the falling out or thinning of the hair, gives a curious aspect.

Fever.—This may be regarded as practically a constant feature of the disease. The average duration of fever in this series was thirty-one days.

Fig. 3.

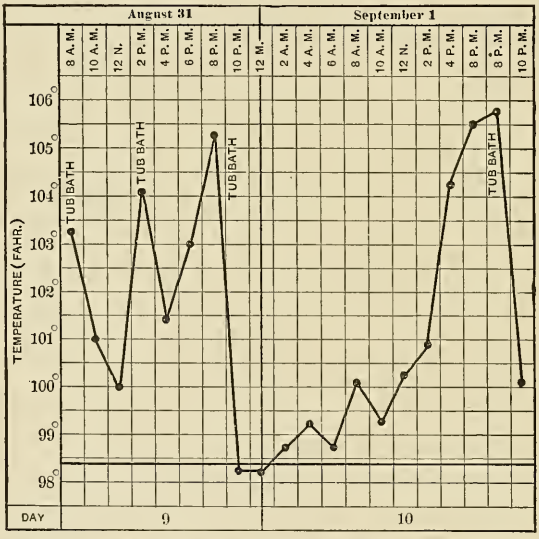


Termination by crisis.

In 1,118 the temperature reached 104° F. or over, in 643 the maximum was from 104° to 105° F., in 411 from 105° to 106°, in 58 from 106° to 107° F., and in 6 over 107° F. In only 25 per cent. did the temperature remain below 104° F. throughout the attack. The classical description of the fever of onset is of a gradual step-like rise, the temperature each evening being

higher than on the preceding one but usually lower in the mornings than in the evenings. As already noted this is not constant and in some instances the elevation may be rapid. The fever, as a rule, reaches its height from about the seventh to the tenth day and then persists in a fairly steady line. But there is no constant rule and we see every variety of temperature chart. Toward the end of the attack, and especially in the third week in ordinary cases, the temperature begins to show remissions. Under the bath treatment these are especially marked after the tubs, falls of three and four degrees being not uncommon. The effect of hydrotherapy on the temperature varies greatly and some patients respond markedly to any form. The remissions are at first in the morning and for many days the temperature may go above 102° F. only in the afternoon. At this stage the highest temperature is generally about four or six in the afternoon. The termination is usually by lysis, although rarely it may be by crisis as in two of this series (Fig. 3).

Fig. 4.



Showing a marked drop after a tub bath early in the disease. The temperature was normal on the twenty-second day.

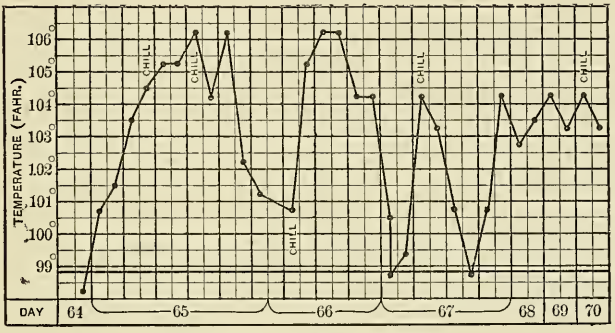
It is well to bear in mind that the temperature curve may show many variations. In some the temperature may fall to normal and remain so for as long as twelve hours. This may occur early in the attack and is worthy of note as in a doubtful case with fever for some days such a record would seem to rule out typhoid fever. Such mistakes make one cautious in attaching too much importance to such a drop (Fig. 4). It is stated that in some cases an inverse type of fever occurs, higher in the morning than in the evening, said to be common in patients who work during the night and sleep in the day.

Sudden changes in temperature may occur. These should always suggest the possibility of some complication but they are frequently seen without any cause being found. With the baths there may be marked falls in temperature which as a rule do not last long. With hemorrhage there is usually some

drop in temperature which may be ten degrees. A sudden fall is not characteristic of perforation, although it may occur, but just as frequently there is elevation for a few hours which may be followed by a drop. In the latter part of the attack there may be marked variations. Extreme hyperpyrexia is not common. The temperature rose above 106° F. in 64 out of the 1,500 cases and above 107° in 6. Just before death the temperature may rise to 108° or 110° F.

The fever of the relapse may be practically a repetition of that in the original attack with the same gradual step-like ascent but in some the temperature may rise rapidly (Fig. 5). This is especially likely if the onset of the relapse is with a chill or with some complication. The duration of the

Fig. 5.



Sudden onset of relapse with chills.

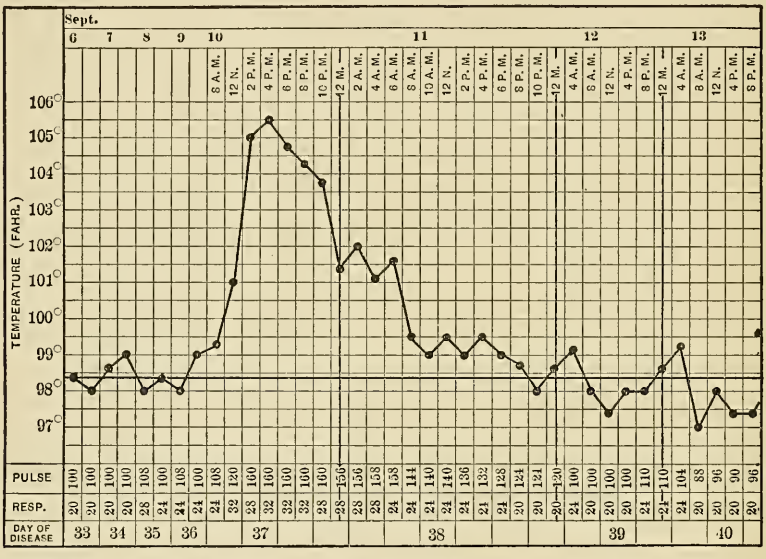
fever in the relapse is usually shorter than in the original attack although it may be longer. The fever of the recrudescence is of short duration and rarely rises very high, 101° or 102° F. being the maximum.

The temperature curve in convalescence may show two variations, one a slight persistent fever and the other a subnormal temperature. The slight fever, averaging from 99° to 100° F. is often very troublesome, as it may last for weeks, sometimes with the patient steadily improving, at other times with the condition almost stationary. Such a type of fever always demands frequent careful examination to exclude a complication. Pleurisy, a slight phlebitis or a bone lesion may be the explanation. Constipation is sometimes a cause and many of these patients have a heavily furred tongue. In others too early an increase in diet is the cause of the fever, as can be shown by going back to liquid food. In others it may be due to a nervous condition or to anæmia. In children this slight grade of fever is more common and of less significance. If a complication can be excluded, the patient's general condition be good and the tongue clean, it is often well to either discontinue the taking of the temperature or take it only once or twice a day. In such cases the diet can usually be increased with safety.

Hypothermia in convalescence is quite common. For days the temperature may not rise above 97° F. This is seen especially after protracted attacks or when there has been great emaciation. It usually does not persist for more than two weeks and is of no special significance. It was present in 168 out of 585 cases (28 per cent.) which were specially studied in reference to this point.

Post-typhoid elevations are by no means uncommon and may occur at any stage of convalescence. They were present in 92 of this series. They cause anxiety, as one always fears a complication. They may be accompanied by chills but as a rule the only feature is the sudden sharp rise of temperature which may be to 104° or 105° F. It may fall to normal in a few hours or may persist longer, though rarely more than twenty-four hours. It may be impossible to find any cause; constipation, excitement or the eating of solid food may be factors (Fig. 6). In some cases the elevations occur with chills.

Fig. 6.



Elevation of temperature and rapid pulse in convalescence due to the eating of fruit.

Chills.—These are by no means infrequent and may occur under various conditions:

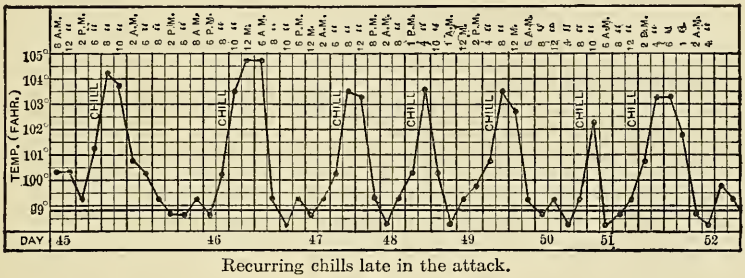
1. **At Onset.**—This was the case in 334 of this series and often gives much difficulty in diagnosis, especially in a district where malarial fever is common. They may also occur at the onset of a relapse.

2. **With Complications.**—This may be at the onset of pneumonia, pleurisy, otitis media, perforation, hemorrhage, phlebitis, periostitis, suppuration, etc. It is this which makes the occurrence of a chill during the course always a disturbing matter on account of the fear that it may be due to some complication. They may occur in instances of "septic infection." A chill may occur with hyperpyrexia sometimes without any explanation.

3. **In Convalescence Without any Complication** (Fig. 7).—It is difficult to give the cause in the majority of these. There may be repeated chills with high elevation of temperature. In one of this series at the time of each chill typhoid bacilli were grown from the blood (Fig. 8), and this may be the explanation for some of them. Constipation has been suggested as a cause but this seems doubtful.

4. **With Treatment by the Antipyretic Drugs.**—This is not rare, especially if the coal tar products are given. The application of guiacol may cause them. Special attention has been drawn to this by Janeway.

FIG. 7.

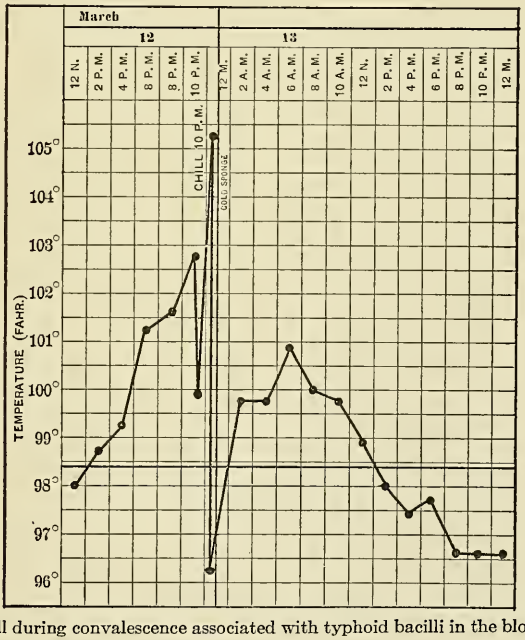


Recurring chills late in the attack.

5. In some cases they occur at intervals through the entire course, perhaps with profuse sweating, and no explanation is found.

6. During convalescence they may occur in the rare instances of combined infection with typhoid and malarial fevers, and sometimes after severe attacks.

FIG. 8.



Chill during convalescence associated with typhoid bacilli in the blood.

7. After the injection of serum.

The character of the chill in any of these may be very severe, and profuse sweating may follow. Their occurrence should always suggest a careful examination for a possible complication. In some they may be due to a secondary infection.

The Skin.—The skin manifestations are especially important for diagnosis. The characteristic rash appears in the form of small, rounded circumscribed red areas, termed the roseola or rose spots. They are slightly raised, of a pale-red color at first, later becoming darker. They can usually be felt by the finger, disappear on pressure and as a rule are discrete, although in rare instances they may coalesce. The diameter averages from 2 to 4 mm. They usually appear from the seventh to the tenth day and are rarely seen at the beginning of the attack. They generally come out in successive crops, and after a few days, usually three to five, fade away, not infrequently leaving behind a faint brownish stain. The rash is very variable in its time of appearance, duration and extent. It may not appear until late in the attack or even after the temperature has become normal, as in 21 cases of this series. The longest interval between the beginning of apyrexia and the first appearance of the rash was fourteen days. It is well to keep this in mind, as the advocates of special methods of treatment have laid great stress on the first appearance of the rash after the temperature had become normal. Occasionally the rash may not be present in the original attack but comes out in the relapse as in 3 cases of this series. The length of time during which successive crops may appear is variable. There may be only a few spots seen at one time or there may be an abundant eruption throughout the whole course of a long attack. In some patients with the rose spots present during pyrexia, fresh ones may continue to appear after the temperature is normal. The number of spots is also very variable. In some only 3 or 4 may be found during the whole attack or they may be present in large numbers. Perhaps 10 to 20 may be given as the average number present at one time but they may be very numerous, even 200 or more. The position of the spots shows considerable variation. As a rule they are most abundant on the abdomen and lower thorax but are not uncommon on the back and should always be carefully looked for there if none are found on the front of the body. In some they may be seen on the neck and face, on the arms and hands, or on the legs. They may be found only on the arms and about the thorax. A very profuse eruption is not necessarily associated with a severe attack. The general character of the rash may vary from year to year; during one season rose spots may be very few, while in almost every patient in the following year the rash may be profuse.

There is rarely much difficulty in the recognition of typical rose spots but at times there may be some question as to the nature of suspicious spots. It is helpful to mark them so that they can be observed on succeeding days. Similar spots may be found with trichinosis and have been reported in acute miliary tuberculosis but with these diseases they apparently do not come out in successive crops. An atypical typhus fever rash may much resemble that of typhoid fever. Insect bites should not be mistaken as they usually show a central point of hemorrhage. A few acne-like spots may give the greatest difficulty in recognition.

Rose spots were present in 1,205 of this series (80 per cent.). This included both white and colored patients; among the 1,233 white patients they were found in 1,150 (93.2 per cent.) while among the 267 colored patients they were found in 55 (20.6 per cent.). In the very dark colored patients it is not often possible to recognize them but they can be seen in those with lighter skins as darker areas on the surface. Palpation is sometimes an aid in their recognition. The rash was noted as exceptionally profuse in 164 patients.

Of these it was on the arms in 81, forearms in 17, hands in 3, thighs in 43, legs in 15, about the knees in 3, ankles in 1, feet in 2, shoulders in 9, axilla in 1, neck in 6, face in 5 and on the scalp in 2.

In some patients the rose spots may be capped by small vesicles, and subsequently scabs may form over these. Some writers describe "pustular rose spots." Pustules are often found on the buttocks. In a certain number purpuric spots appear, as in 38 of this series. The rose spots may become purpuric or may be hemorrhagic on the first appearance, apart from those seen in the hemorrhagic type. Toward the latter part of the attack there may be quite marked desquamation. This varies considerably from year to year, and in the last two years here, it has occurred in an unusual number of cases. It may sometimes be quite marked over the abdomen even when no local application, such as turpentine stupes, has been used.

Among other skin lesions in typhoid fever the following may be noted:

1. **Erythema.**—It is not uncommon to find areas of erythema early in the disease, which may be specially about the joints. It is of no special significance although in rare instances it may give difficulty in diagnosis at the onset. It was present during the course of the disease in 15 of this series. If drugs, such as quinine, are given, erythema may be more frequent. Erythema nodosum may be present; in one patient it appeared at the onset. Erythema multiforme has been reported. Unusual rashes have been described, as in a patient of Rolleston's, who under the name of "an anomalous superficial dermatitis" reports a curious eruption which began as erythematous macules and later was suggestive of psoriasis. Ecthyma was present in one patient of this series, who possibly had congenital syphilis. It disappeared under iodide of potassium.

2. **Urticaria.**—This occurs rarely and is more likely to be present when drugs are given. It was noted in only 2 of this series.

3. **Hemorrhagic Rash.**—Some variety of this is not uncommon. In 38 cases purpuric spots were noted; in the majority of these, typical rose spots first appeared which later became hemorrhagic. In 9 cases the rash was regarded as hemorrhagic, 3 of these being the hemorrhagic type of the disease. In severe cases ecchymoses may appear, especially in the dependent parts.

4. **Herpes.**—This is rare, especially in comparison with its frequency in various other febrile affections. It was noted in 20 cases of this series, of which 18 were at the onset. As a rule herpes appears in the first week and is on the lips, but it has been reported elsewhere on the body.

5. **Pemphigoid Rash.**—This was noted in one case.

6. **Peliomata or Taches Bleuâtres.**—These are bluish gray subcuticular areas from 4 to 10 mm. in diameter. They are situated most commonly on the lower abdomen, the pubic region and upper thighs. For a long time considered as almost specific evidence of the disease, it is established beyond a doubt that they are always associated with the presence of pediculi and are not peculiar to typhoid fever. The importance attached to them as a supposed sign of the disease is a striking example of the fallability of human observation and judgment.

7. **Miliary Eruption.**—This occurs fairly frequently in typhoid fever, in the form of round vesicles usually about the size of the head of a pin and occasionally showing coalescence. If profuse the rash gives a very striking appearance. No special significance is to be attached to its occurrence.

As a rule the eruption is most marked on the abdomen and sometimes on the chest.

8. **Ulcers.**—In a few instances, especially in children, these may be multiple, varying in diameter from 3 to 10 mm. In one patient they were very numerous and no cause for their formation could be found.

9. **Gangrene.**—This may occur in special epidemics but as a rule is a rare complication. There may be multiple areas of superficial gangrene of the skin and in children noma may occur. It occasionally happens that a small area of superficial gangrene occurs on the abdomen if an ice-bag has been kept applied for a long time.

10. **Furuncles.**—These are troublesome and by no means rare. Their most frequent situation is on the back and about the shoulder and gluteal region, although they may be found anywhere, as in the auditory canal where they cause much suffering. They may be present during the fever, especially in protracted attacks, but are most likely to appear in convalescence. As a rule more troublesome than dangerous, yet they may cause great suffering and in debilitated individuals prolong convalescence. While rarely the cause of death, yet in some cases there seems no question as to their being the source of a terminal general infection. The organism found in the boils is usually either a streptococcus or a staphylococcus. The typhoid bacillus was not found in any of this series, although there are some cases in the literature. The occurrence of boils is thought by some writers to be more frequent with the bath treatment. It is certainly important when baths are being given to isolate the tubs which are used for the patients with boils.

11. **Abscesses.**—These may occur during the attack but are more frequent toward the latter part of the illness and during early convalescence. They are sometimes responsible for elevations of temperature. The character and size of the abscess may vary greatly. There are some which are small and superficial and much like boils. They are not uncommon in the perirectal tissues. If hypodermic injections or saline infusions have been given, abscesses may form about these situations especially in debilitated individuals.

12. **Bed-sores.**—The frequency with which these occur has steadily diminished with better care and nursing. As a rule they occur in the sacral regions but in rare cases may occur on the heel, in the scapular region or about the elbow. They are less common under the bath treatment. Incontinence of urine or fæces strongly predisposes to their development while patients with hemorrhage who are kept absolutely quiet are prone to them. The physician should make it a part of his routine examination to examine the back every day.

There are different kinds of bed-sores. The commonest is that which occurs in the sacral region. The skin shows a little redness, then there is some loss of superficial tissue with discoloration beneath and usually after this a line of demarcation appears followed by the separation of a central slough. The amount of damage is very variable; only the skin and subcutaneous tissue may be involved or the process may go much deeper. It often happens that sound skin has been undermined and much more destruction has occurred than appears on the surface. Another type is termed by Curschmann the subcutaneous one, which does not always develop in areas subjected to the greatest pressure. As a rule the process begins in the subcutaneous tissues, the skin gradually becomes discolored, softening goes on

and finally there is the discharge of dirty, often sanious, pus. There may be several discharging sinuses and in such cases there may be destruction of a large amount of tissue and the necrosis extends to the bone. This is especially likely to occur in the profoundly toxic patients. It is doubtful in certain patients if any care can prevent the development of this form of bed-sores and it seems well to emphasize this, as the statement occasionally made, that the nurse is always to blame when a bed-sore develops, is not true.

13. **Lineæ Atrophicæ.**—These may appear very abundantly, as after any acute illness. They are especially frequent over the lower abdomen and thighs but may be seen about the shoulders or knees. Certain cases may be due to neuritis but as a rule they are probably the result of mechanical changes.

14. **Hair and Nails.**—It is very common for the hair to fall out after the attack. This seems less likely to occur if it has been cut short at the beginning of the illness. If the hair has been lost the new growth takes place slowly. Permanent baldness has occurred but is rare. The nail usually shows a marked groove which appears as the nail grows out.

15. **Odor.**—In some patients there is a very characteristic odor which is often described as mousy or having a musty quality. It is sometimes most noticeable in the palms of the hands. Under active hydrotherapy it is probably less frequent but seems to be a peculiarity of certain patients and may be present during the attack and well into convalescence. Some of the older writers attached great importance to it in diagnosis.

16. **Sweating.**—This is not common at the onset, especially if there be chills or chilly sensations. During the course it is rare except with some of the complications. With hemorrhage or perforation the patient may sweat most profusely. In convalescence it may occur with the post-typhoid chills.

17. **Pigmentation of the Hands and Feet.**—In some patients there is a marked yellow color of the palms of the hands and soles of the feet, which is usually most marked toward the latter part of the attack. It does not seem to have any special significance.

The Digestive System.—The mouth usually shows certain changes. There is a tendency to dryness of the mucous membrane and often some swelling of the tongue which shows indentations of the teeth. The tongue is usually coated with a white fur which later on may become very thick. In severe cases the tongue becomes dry, covered with a dark fur and may show fissures which bleed readily. With this the teeth may be covered by sordes and also the lips, which may be cracked and bleed. These are due to several factors, the fever, lessened secretion, breathing through the mouth and diminished movements of the tongue. With the giving of large amounts of water internally, and regular attention to the mouth locally, the tongue may remain moist and only lightly coated while the lips remain practically normal The condition of the mouth is often a good index of the care which the patient is receiving. In very severe attacks when the care of the mouth has been neglected, thrush may develop. This may involve the mouth and pharynx. A diphtheroid membrane may be found. In one patient of this series there was a diphtheritic membrane on the lip from which the Klebs-Loeffler bacillus was obtained. Stomatitis occurs occasionally and ulceration of the mouth and circumscribed gangrene have been noted. Noma occurs rarely, usually in children.

Acute Glossitis.—This is rare and occurred only once in this series at the onset of a relapse. This complication is not likely to be serious, as the swelling can be readily diminished by incision into the tongue or by drawing blood from it by a needle.

Parotitis.—This is an important complication which occurred in 14 of this series (.9 per cent.), which is about the frequency found in larger statistics. Among 12,173 cases (London Fever Hospitals, Hoffmann, J. McCrae and the present series) it occurred in 93 (.7 per cent.). It is thought to have become rarer in recent years owing to the greater care given to the mouth. It is more likely to occur in severe attacks. The infection may be by direct extension along the duct from the mouth or through the blood. It may be part of a general infection, a general infection may follow it, or serious intracranial complications, such as thrombosis, may result. It usually appears in the third week or later, and in some instances during convalescence. The clinical features do not differ from secondary parotitis under other conditions and as a rule it is unilateral. If both parotids are involved one usually follows the other. The swelling appears first behind the angle of the jaw and may increase very rapidly. The skin over it is usually red and there is marked induration and tenderness. There may be a chill with the onset and the temperature usually becomes higher. There is generally severe pain. The course is variable and in some the swelling subsides but in others suppuration or gangrene occurs. Early incision is advisable if there are any signs of suppuration. Marked necrosis is found in some and the greater part of the gland may slough away. There are instances of extension of the process to the structures of the neck, even to the mediastinum.

The organism present is usually either the streptococcus or staphylococcus. The typhoid bacillus may be associated with these or found in pure culture. In some cases on early incision no pus is found but cover-slips and cultures show large numbers of streptococci. Typhoid bacilli were not obtained in any of this series. It may be possible to obtain cultures from the parotid duct; a very fine sterile glass tube may be introduced into the duct and a wire passed inside of this from which the cultures are made.

The condition is serious. Death occurred in 5 among 14 cases in this series and the mortality of reported cases is about 30 per cent. This is partly due to the occurrence of parotitis in severe attacks. In case of recovery the swelling usually persists for about a week. After recovery there may be persistent enlargement and induration of the gland. In some instances there may be deformity from the amount of destruction, and facial paralysis has been noted. In one of this series persistent sweating in the parotid region, during eating, followed an abscess.

Submaxillary Glands.—These may show involvement as in 4 patients of this series, of whom 3 died. Streptococci were found in 2 and typhoid bacilli and staphylococci in 1. In 1 a marked angina followed and in 1 both glands were involved. As a rule, involvement of the submaxillary glands is not as serious as parotitis.

The Pharynx.—Involvement of the throat is rare in typhoid fever. Early in the disease there may be slight inflammation with congestion, or membranous pharyngitis may appear later. Usually in severe cases the pharynx shares in the dryness of the mouth and may then be covered with a very tough mucus which the patient is unable to cough up and which often gives a great deal of discomfort. There are instances of ulceration of the palate,

tonsils and pharynx, which may occur early in the attack and in 3 out of 4 such cases reported by Marquordt from Ebstein's clinic, typhoid bacilli were obtained. Probably they would be more frequently noted if routine examinations of the pharynx were made with more care. Diphtheria may co-exist with the typhoid infection and Klebs-Loeffler bacilli be found. Hemorrhage has occurred from the tonsil.

Angina.—This is exceedingly rare and may extend from lesions in the pharynx or, as in one of this series, from a submaxillary gland. The swelling in the neck may be extreme, it is apt to have a boggy resistant feel and there may be some interference with respiration. The only instance in this series was a young adult who died suddenly without any signs of obstruction in breathing. There were numerous small foci of suppuration through the structures of the neck.

The Œsophagus.—Lesions here are rare and were considered to be more important by Louis (who found ulcers in 7 among 46 cases) than perhaps by any subsequent writer. In the autopsy records of 2,544 cases (Munich Ouskow, and the present series) ulcers were found in the œsophagus in 4. They were present in 3 of 105 autopsies in this series. Typhoid bacilli have been found in the ulcers and there seems no reason to doubt that the ulcers in some cases are specific although in others they are due to secondary infection. They may cause difficulty in swallowing but this may be due also to lesions in the pharynx. Their presence may be suspected when the patient seems to suffer pain when swallowing, although he may be so toxic as to make no complaint. Hæmatemesis may occur. Œsophagismus has been reported without any cause being found at autopsy. Superficial erosions have been found at autopsy but it is doubtful if they cause any symptoms. In 2 of this series at autopsy a diphtheroid membrane was found on the œsophagus and in 1 there was an acute œsophagitis with hemorrhagic areas and much destruction of the mucosa.

Stricture of the œsophagus is one of the rare sequels of the disease. There was one instance in this series. Several cases are reported in the literature, the history usually being of difficulty in swallowing coming on during convalescence and first noted when solid food was taken. The condition has been relieved by dilatation or operation.

The Stomach.—As a rule gastric disturbances are not common. At the onset there may be nausea and vomiting, especially in children, but these rarely persist, although protracted vomiting occurs occasionally. Sometimes gastric distress is complained of without either severe pain or vomiting. Hiccough is rare and generally associated with a complication, especially perforation. During the height of the disease vomiting occurs so seldom that we regard it as suggestive of a complication. It may be from improper feeding, too much water or the giving of drugs. Occasionally vomiting is due to ulcers in the stomach from which bleeding may occur and erosions may be found at autopsy from which it is possible that there may have been oozing. Hæmatemesis occurred in 4 of this series. In rare cases an ordinary round ulcer may be present and in one patient death was due to hemorrhage from a simple gastric ulcer. Perforation of a typhoid ulcer in the stomach has occurred. Rare instances are reported of severe vomiting during convalescence, which has led to a fatal termination. In convalescence, dietetic errors may be responsible for nausea and vomiting. There may be marked distension of the stomach with gas, often associated with intestinal

meteorism, which may cause marked interference with breathing. Acute dilatation of the stomach occurred as a terminal event in one patient.

As a rule there is complete loss of appetite, usually from the onset as in 825 of this series, and almost invariably during the course. In some instances the patient may have a fair appetite throughout the whole attack or even be extremely hungry.

Intestines.—The intestinal features may vary greatly from year to year but it should always be kept in mind that disturbances may be due to meddling. The less interference there is with the bowels, the less trouble there will be with them. During the course of the disease the bowels were regular in 465 (31 per cent.) and constipation was present in 766 (51 per cent.) of this series, making a total of 82 per cent. without any intestinal disturbance. The diet is an important matter and disturbed conditions of the bowels may be due to improper feeding. Much importance has been attached to the gurgling so frequently found in the right iliac fossa, often accompanied with slight tenderness but it is doubtful if this is of any moment. The same condition is found in other diseases.

The stools should be examined as a routine. In many patients the gross character shows nothing characteristic. If the bowels are loose we usually see what is regarded as the typical typhoid or "pea soup" stools. These are peculiar in appearance, thin, of a brownish color and may have a curious, almost characteristic, odor. After standing they separate into two layers, the upper liquid and the lower more solid. Microscopic examination may show portions of sloughs and red blood cells. Occult blood is not uncommon, usually in the third or fourth week. It may be found some days before a hemorrhage and at times well into convalescence. Occasionally green stools are passed, the color being due to biliverdin.

Diarrhœa.—This was present during the course in 260 patients (17.4 per cent.) and in less than one-third of these was it severe. The number of stools with diarrhœa is usually from 4 to 6 *per diem* though as many as 10 or even more may be passed but this frequency rarely lasts long. The diarrhœa which is so frequent at onset—34.4 per cent.—is usually explained as being due to simple intestinal catarrh but the action of purgatives and the influence of diet must be added. Impure milk may be the cause and broths or beef tea frequently seem to set up diarrhœa. During the course of the disease it may be due to ulceration. Instances of very severe persistent diarrhœa are sometimes associated with extensive ulceration in the colon. In some patients the diarrhœa is thought to be of a toxic character. Severe diarrhœa must be regarded as a grave condition for it usually means deep ulceration and severe toxæmia. In some cases the stools have a dysenteric character. This is usually associated with severe lesions in the colon which may be diphtheroid.

Constipation.—This was the rule in 766 of the series (51 per cent.). It seems to be the most favorable condition for the patient. If the bowels are not moved frequently enough by enema, fæcal impaction may occasionally occur but this can be prevented by care. Abdominal pain during the course and slight elevations of temperature in convalescence may be caused by constipation but are easily managed.

Meteorism.—The descriptions of the older writers suggest a frequency much greater than we have today. Not frequent early in the disease, as a rule it is most common at the height of the attack when it is of considerable

gravity because it indicates severe toxæmia and probably increases the dangers of other intestinal complications. By its mechanical pressure on the diaphragm it may seriously interfere with respiration and the action of a weak heart. The distension is usually greatest in the colon but the small intestine and the stomach may be involved. The influence of opium in favoring the production of meteorism must not be forgotten, and is one of the arguments against its use in typhoid fever. Abdominal pain, hemorrhage and perforation may all occur with distension.

Abdominal Pain.—This is present in a large number of cases at some period of the attack. With the onset it occurred in 443 or 29.5 per cent. which does not include the cases in which tenderness only was present. A series of 500 cases was specially studied with reference to this symptom with the following results:

1. Without pain or tenderness at any time—206 or 41 per cent. In this group were instances of several of the abdominal complications but none of perforation. Nine cases of hemorrhage and 1 of abscess of the liver were included. As a rule the cases were of a mild type as was shown by the small number of deaths, namely 8.

2. With tenderness but no pain—72 or 14 per cent. These showed no special features, the common position of tenderness being the right iliac fossa.

3. Pain present—222 or 44 per cent. In 61 of these the pain was present only at the onset, which leaves 161 or 32 per cent. with pain during the course. Some patients may be so dull or delirious that no complaint of pain is made but if they are carefully watched some indications can often be observed. The conditions under which pain occurs may be grouped under several heads:

(*a*) *Those which are apart from any lesion of the disease,* such as hysteria, neurotic conditions, hyperæsthesia, lung and pleural conditions, pericarditis, hepatic or renal colic, distension of the bladder, cystitis, menstruation, labor and abortion. Pain in neurotic patients occurs at times without any cause being found. It is more common in those who are active and alert mentally than in those who are dull and stupid. Pneumonia and pleurisy may cause abdominal pain as they sometimes do apart from typhoid fever. Distension of the bladder is not uncommon but the patients rarely make complaint of pain. In the rare cases in women when menstruation is present, there may be pain. The conditions of this group are usually readily recognized and the most important factor in this is a careful examination.

(*b*) *Conditions of the Alimentary Tract Apart from Complications.*—These include improper feeding, vomiting, colic, diarrhœa and constipation. Severe pain may follow the taking of solid food during the course. Pain with vomiting always suggests some complication. When it occurs with diarrhœa it may be like that of colic and not continuous, being felt just before the stool or while the bowels are moving. Pain due to constipation may be caused by fæcal impaction which is a cause more often toward the end of the attack. The giving of an enema or an irrigation may cause pain. The recognition of the cause is usually not difficult in this group.

(*c*) *Abdominal Conditions Apart from the Specific Bowel Lesions.*—Among these are appendicitis, peritonitis (other than that due to perforation), cholecystitis, intussusception, intestinal obstruction, meteorism, liver abscess, suppurating mesenteric glands, painful spleen and phlebitis, especially of the iliac veins. Pain due to the first three requires no discussion.

Obstruction of the bowels is rare in typhoid fever. Pain in the region of the spleen is not uncommon and may be present even when the spleen is not palpable. Old adhesions may be a factor. The pain of iliac phlebitis may be very severe and not yield readily to ordinary treatment. In 2 patients of this series the abdomen was opened for this cause. The recognition of the cases in this group may be most difficult and in some an exploration is the only means by which it can be determined. Fortunately for many of these doubtful cases laparotomy is essential for treatment.

(*d*) *Hemorrhage and Perforation.*—These will be discussed in the special sections dealing with them.

(*e*) *Without any Cause Being Found.*—This is a large and important group, including 70 of the 161 cases with pain. In certain of these the pain was severe but as a rule not prolonged. Some are of special interest, in that with marked abdominal features there was a leukocytosis varying from 10,000 to 17,000. Exploration in one showed no cause, in another signs of an early peritonitis were found. In 2 no cause could be found at autopsy. The explanation in the majority of this group is difficult to give. A local peritonitis must be rare and at the most could only account for a small number. That deep ulceration is a frequent cause of pain does not seem likely. Certainly it is not constant when we remember the number of patients with deep ulceration at autopsy but without any pain during life. It may be that the inflamed serosa over an ulcer causes pain, but this is not usual judging from experience with patients operated on under cocaine, who as a rule do not make any complaint of pain when the peritoneum over an ulcer is touched. In one patient any pressure at operation over one ulcer gave severe pain although his eyes were bandaged so that he could not see when the bowel was touched. Whether enlarged mesenteric glands may be a cause of pain is hard to decide. Patients operated on under cocaine have not made any complaint when the glands were touched.

No explanation can be given in many of the cases. In the inflammatory conditions, distended bladder, etc., the reason is evident. But why there should be pain with hemorrhage or distension is not clear. Lymphangitis has been suggested as an explanation in some instances. Patients who have had pain for some days and then have a sudden increase give difficulty in diagnosis. In these instances of pain for some days before perforation, it may be suggested that this was due to the so-called "preperforative stage" but of this we have no proof.

The occurrence of abdominal pain should always be regarded as a danger signal, demanding careful examination. The "extra-abdominal" conditions are usually easily ruled out, the others may give great difficulty. The patient should be studied with perforation in view—it is well to be prepared to recognize the most serious possibility. If there are marked features suggestive of a complication and the attendant means to operate himself, everything should be in readiness so that no time may be lost if the need arises. If a surgeon is to be called, he should be given the chance of seeing the patient early so that he may be able to decide not only whether he shall operate or not but *when*. To call the surgeon after general peritonitis has appeared is not fair to the patient or to him.

One other point deserves emphasis—*opium should not be given for abdominal pain in typhoid fever*. Give opium and all chance of early recognition of the most important complication is gone. A quotation from Macauley

may be given although he was writing of different conditions: "Profound and ingenious policy. Instead of curing the disease, to remove those symptoms by which alone its nature can be known. To leave the serpent his deadly sting and deprive him only of his warning rattle."

Hemorrhage.—As a rule we only consider bleeding from the bowels under this heading, although in rare instances—3 of this series—there may be profuse gastric hemorrhage, apart from that in the hemorrhagic type or from an ordinary gastric ulcer. It is well to make a distinction between the cases in which only a small amount of blood is passed and those in which there is a considerable quantity, as it is by no means rare for patients to pass small amounts of fresh blood with a stool. This may be in the form of streaks over the surface of the fæces from hæmorrhoids or a fissure. This is usually small in amount and of a bright red color. Such should not be considered as hemorrhages. Occasionally patients pass small amounts of altered blood or a single small clot, the amount of blood not being more than a few cubic centimeters. If the stools are carefully examined these will be found fairly often but such can hardly be termed cases of hemorrhage. There is always difficulty in comparing the statistics regarding hemorrhage unless it is stated whether or not this group is included. However these patients should always be watched carefully as one is never sure that severe hemorrhage may not follow later.

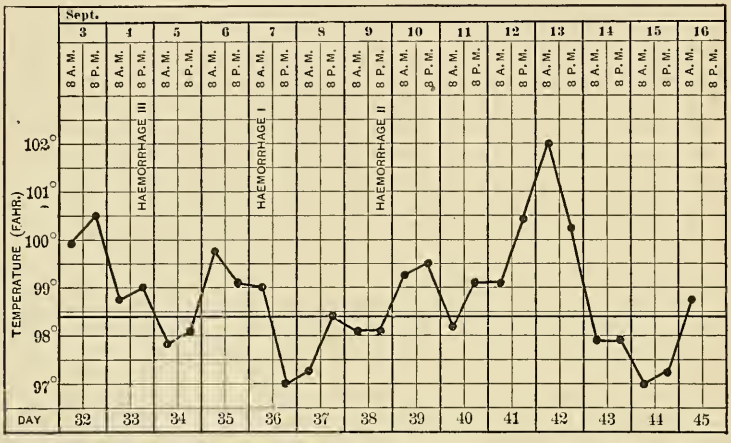
The frequency varies in different statistics and the average of a large number of cases is about 7 per cent. It occurred in 118 cases of this series (7.8 per cent.). J. McCrae, among 717 cases in the Montreal General Hospital found it in 72 (10 per cent.), Strümpell in 45 of 472 cases, Curschmann in 103 among 1,626, Greisinger 32 among 600, Homolle collected 465 among 10,000, and the London Fever Hospitals had 706 among 8,356 cases. Among the total of 23,271 cases there were 1,641 of hemorrhage (7 per cent.). The figures may vary widely from year to year in the same clinic. Certain families seem to be very prone to it. Children rarely have hemorrhage.

A distinction should be made between the early hemorrhages, which are rarely serious, and the more frequent later ones. The former are probably due to oozing from the hyperæmic patches and the amount is usually small. It may have been the prevalence of this variety which led some of the earlier writers, such as Graves and Murchison, to regard hemorrhage as sometimes almost favorable. The ordinary hemorrhage during the course is a serious complication. The amount of blood lost may vary from a few cubic centimeters to a liter and there may be one large hemorrhage or repeated ones of varying amount. The patient's general condition may show no change or he may become exsanguine and be in a state of profound shock, with subnormal temperature, profuse sweating, cold extremities and a rapid feeble pulse. There are all variations between these two extremes.

The time of most frequent occurrence is toward the end of the second and through the third week. Of the cases in this series in which the time of the first hemorrhage was definitely known, 1 was in the first week, 22 in the second, 38 in the third, 20 in the fourth, 13 in the fifth, 4 in the sixth and 1 in the seventh week. The latest day was the forty-third. In one patient the temperature had been normal for eleven days before the occurrence of a hemorrhage of 200 cc. In another a hemorrhage of 500 cc. was on the last

day of fever in the primary attack, a relapse beginning five days later. They may occur with the temperature almost normal (Fig. 9). The greatest interval between the first and last hemorrhage was fourteen days, in a patient who lost small amounts on the eighth and twenty-third days. In another there were five large hemorrhages between the twenty-fourth and thirty-eighth days. Another with seven hemorrhages between the twelfth and twenty-fifth days lost 2,250 cc. It seems to occur relatively infrequently in a relapse (only in 2 of this series among 173 cases).

FIG. 9.



Showing repeated hemorrhages with the temperature almost normal before their appearance.

The number of hemorrhages varies. Of the cases with definite notes, 1 hemorrhage occurred in 48, 2 in 18, 3 in 11, 4 in 8, 5 in 6, 6, 7 and 10 in 2, 8, 9 and 11 in 1 each. In 6 the bleeding was more or less continuous and the number could not be estimated. The passage of blood from the bowel is the only positive proof we have of hemorrhage but this does not necessarily give a correct idea of the bleeding, for after repeated small hemorrhages only one bloody stool is passed, or part of the blood from one hemorrhage is passed fairly fresh and the remainder much altered several days later. The largest total amount passed by any of the patients was 2,550 cc. in five hemorrhages during a period of fourteen days. Another lost 2,000 cc. in three hemorrhages. Twelve lost over a liter of blood.

As regards any exciting cause for hemorrhage we can say little. It may be the first symptom in an ambulatory case. With careful feeding the diet does not seem likely to be a cause, although it is possible that the taking of solid food too early might have some influence. There is no proof that hemorrhage occurs more frequently under the bath treatment. Sometimes blood may come with an irrigation or enema as happened in 12 patients (not including those in which the enema was given some days after a hemorrhage and brought away altered blood) but in none was the quantity over 100 cc. There is usually no warning of hemorrhage beforehand. At times it is suggested by the patient suddenly becoming very restless, an altered appearance or sweating. Sometimes the pulse shows a marked change, not so much in the rate, although this may be increased, as in a curious bounding

quality, which may make one almost sure that hemorrhage has occurred, hours before any blood is passed from the bowel.

The symptoms depend on several factors, the condition of the patient, the amount and rate of the bleeding and the number of hemorrhages. Thus in a strong, robust individual one moderately large hemorrhage or several small ones may have no effect on the general condition while in one who is debilitated a moderate loss may make a profound change. However, even a moderate hemorrhage usually has some effect on any patient. In an average case there is pallor, the surface and extremities are cold and sweating may be present. Vomiting, sometimes of blood, may occur. The patient may complain of weakness. The temperature usually falls and the drop may be as much as 10° and to below normal. Still even a sharp hemorrhage may have no effect on the temperature. The pulse rate rises and with it the quality alters. At first sometimes bounding, later it becomes small and running. The blood pressure falls usually to 80 or 90 mm. Hg. The lowest record in this series was after one sudden hemorrhage of nearly a liter when the blood pressure fell to 55 mm. Hg. The changes in the blood count depend on the previous condition and the amount of blood lost. There is naturally a rapid drop in the hæmoglobin and number of red cells. The fall may be marked, thus in one patient after severe bleeding the hæmoglobin fell from 82 to 40 per cent. and the red cells from 5,000,000 to 3,300,000. In another anæmic patient the hæmoglobin fell from 56 to 27 per cent. and the red cells from 3,000,000 to 1,900,000 within a day. The number of leukocytes may not be altered. If an increase occurs this is usually not extreme, the count rarely exceeding 15,000 per cmm. The highest in this series was 27,900 per cmm. The maximum is usually attained within twenty-four hours, and there is generally a return to normal within a week. In one the leukocytes fell from 11,300 to 3,700 in four days.

A point of importance is the coagulation time of the blood in patients who have hemorrhage. The average for 108 patients of this series, none of whom had hemorrhage or jaundice, was 3.5 minutes. Of these only 7 (6.5 per cent.) had a coagulation time longer than five minutes and only 4 of these were over six minutes. In 3 of these the time was reduced to normal by the use of calcium salts. The average coagulation time of 22 patients with hemorrhage was 4.2 minutes. It was over five minutes in 6 (27 per cent.) and 5 of these were over six minutes. In nearly all of these the time was reduced to normal by the use of calcium salts. These figures are too small for positive conclusions but are suggestive. Severe hemorrhage occurred in patients with normal coagulation time but nearly all the patients with very prolonged coagulation time had profuse hemorrhage.

Abdominal pain with hemorrhage is not uncommon and may be severe. In some it has been present for two or three days before but this may have been only a coincidence. After a hemorrhage it is best to avoid any more examination of the abdomen than is necessary and palpation should be very light. The time when the bleeding actually occurred and the passage of blood from the bowel may be hours or days apart but an idea of the interval can often be obtained by the appearance of the blood. In the large single hemorrhages the stool is usually fluid and reddish in color and in estimating the quantity of blood one must remember how much color a small amount of blood can give to a considerable quantity of liquid. In other instances the stool may consist of fluid and clotted blood. The occurrence of clots

is often regarded as indicating profuse sudden bleeding, probably from a large vessel. In repeated hemorrhages the blood may be fresher in each successive movement from the bowels. If the blood remains some time in the bowel it may be much altered and passed as dark clots. The finding of these in the stools is sometimes the first indication that hemorrhage has occurred.

The results are very various and there is no doubt that some patients do seem to be benefited. These are usually robust and not very toxic. The temperature may be lower, the pulse not increased or even decreased in rate and the whole character of the attack milder. There are two forms which stand out, the large single hemorrhage with marked effects and the repeated smaller ones. The former is rarely fatal for the danger comes from repetition and comparatively few die directly from the bleeding. In collecting statistics of the fatality of hemorrhage there is one source of error as, if all are included who had hemorrhage followed by death at any interval, a false idea of its danger is obtained. Thus a patient may have hemorrhage and die a week later from perforation or after two or three weeks from toxæmia and asthenia, the hemorrhage having contributed only to influence the general condition, or a patient who is very toxic may pass a small amount of blood and die soon after but it is doubtful if the hemorrhage should be considered as the cause of death. The figures given by writers vary widely but the usual statement is that 20 to 30 per cent. of the patients die. Curschmann gives 38 per cent. for his Leipsic series. Among 118 cases in this series there were 12 deaths, only 10 per cent. Of Strümpell's 45 cases, death resulted from the hemorrhage in 8 and 11 died after a time. The figures may vary greatly in different years in the same clinic.

Perforation.—This is the most serious frequent complication. The figures as to its occurrence vary greatly in different autopsy reports. The Munich series of 2,000 autopsies showed perforation in 5.7 per cent., Murchison in 435 autopsies, 13.8 per cent., Curschmann in 575 autopsies, 16 per cent. The figures of Herschel, and Broardel and Thionet among a total of 2,667 autopsies showed perforation in 7 per cent. Mackenzie found that 351 out of 1,037 deaths from typhoid fever in certain London hospitals were due to perforation. In this series of 105 autopsies, perforation was found in 30 (28.5 per cent.) so that among a total of 6,819 autopsies there were 834 cases of perforation (12 per cent.). Of the 137 deaths in this series 33 (24 per cent.) were due to perforation. In recent years many patients are saved who formerly died of toxæmia, whereas we have not reduced the mortality from perforation to a corresponding degree. This is well brought out in the series reported by Hare of Brisbane, for among 1,828 cases treated by the expectant method, perforation occurred in 2.9 per cent. and was the cause of death in 20 per cent. of the fatal cases. Among 1,902 treated by baths the incidence of perforation was the same (2.9 per cent.), but its proportion among the fatal cases rose to nearly 40 per cent.

When we turn to the incidence of perforation in clinical reports we find much more agreement in the statistics. As a rule, hospital figures show perforation in from 2 to 3 per cent. of all cases. German statistics for 6,321 patients (Curschmann, Hamburg records, Griesinger) showed 117 (1.8 per cent.), Murchison in England found 48 among 1,580 (3 per cent.), Mackenzie from London hospitals reports 351 among 9,713 (3.6 per cent.), J. McCrae in 717 in Montreal in 43 (6 per cent.), Hare of Brisbane in 2.9

per cent. of 3,723, the London Fever Hospitals 294 among 8,356 and Scott (Philadelphia) in 84 among 3,006 cases. In this series there were 40 of perforation (2.6 per cent.). The total of these figures gives a percentage of 3.1 among 34,916 cases. When we endeavor to estimate the total number of patients who die from perforation each year the figures are appalling. In the United States census report for 1900 the deaths from typhoid fever are given as 35,379. If 1 death in every 8 was due to perforation we have a total of 4,422.

The incidence of perforation varies greatly from year to year. Several cases may be seen in one clinic within a few weeks, and the successive hundreds of any large series may show a very varying percentage. Thus five cases of this series occurred in one period of six months. Manges reports 19 cases of perforation in 216 cases (8.8 per cent.) from the Mt. Sinai Hospital in New York. As to the influence of sex, perforation occurs more frequently in men. Figures from the literature give the frequency as about 3 males to 1 female, but hospital statistics usually show more males than females. In this series, 32 were males and 8 females, but, taking the number of admissions in each sex, we find that perforation occurred in 1 out of 33 males and 1 out of 55 females, which makes the disparity less. As regards age, perforation rarely occurs below ten years. The largest number are in the third decade. The statistics of Fitz show 24 per cent. in the second, 40 per cent. in the third, and 23 per cent. in the fourth decade. In this series the age was as follows: from one to ten, 3; from ten to twenty, 10; from twenty to thirty, 15; from thirty to forty, 6; and from forty to fifty, 6. Over forty years of age perforation is rare, and in that this series is unusual. The oldest patient was forty-nine years. The children were aged eight, nine and ten years.

The period of greatest incidence is the third week. In this series the distribution was: first week, 0: second, 10; third, 12; fourth, 7; fifth, 5; sixth, 1; seventh, 2; and eighth 1. The latest case was on the fiftieth day. In 2, perforation occurred while the patients were about and the day of disease could not be determined. Instances have been reported as late as the sixteenth week. Perforation may occur after the temperature has become normal and the patient convalescent. This has been brought about in some by the taking of solid food.

The site is most frequently in the ileum. In this series the perforation was in the ileum in 32, the appendix in 3, the sigmoid flexure in 2, the cæcum in 1, and in one both in the descending colon and rectum. Taking the figures of Liebermeister, Mackenzie, Fritz and this series, the site was in the ileum in 506, colon 56, appendix 32, Meckel's diverticulum 4, jejunum 4, cæcum 1, and in one in both the colon and rectum. The number of perforations may vary from 1 to 25 but in the majority there is but 1. Of 39 of this series in which this was determined, there was 1 perforation in 28, 2 in 8, and 3 in 3. Of the 32 in the ileum, in 26 there was 1, in 3, 2, and in 3, 3 perforations. The opening was within 40 cm. of the ileocæcal valve in 27 and the greatest distance from the valve was 150 cm. In 1 case 2 perforations were within 12 cm. of the valve and this was the only instance in which the bowel was so friable that sutures would not hold. Of the 3 with perforation in the appendix, 2 had two openings.

In discussing the symptoms we should separate those due to perforation from those of the resulting peritonitis. If this be local, as it may be for a

few hours after perforation, there is no special change in the general picture, but in the literature until very recently, most of the descriptions of the symptoms of perforation were those of the resulting general peritonitis. It should always be our aim to make the diagnosis of perforation before general peritonitis has come on. The recognition of perforation can as a rule only be made if there has been careful preparation for it. In a hospital the house officers should always be alert and ready to attend whenever there are any suspicious symptoms. The nurses or the members of the family, if the patient is being nursed at home, should be told to report any suspicious symptoms immediately. Of these the most important for diagnosis are sudden abdominal pain, nausea and vomiting, any sudden change in the patient's general condition, especially sweating, or any signs of collapse. The report of any of these should always lead to the careful examination of the patient, with perforation in mind. It cannot be emphasized too strongly that the most important of these is the onset of sudden sharp abdominal pain.

May we have any premonitory symptoms of perforation? In some instances the symptoms suggest slight local peritonitis before perforation but this is difficult of proof. Some patients have abdominal pains for days before perforation occurs but when we remember the frequency of abdominal pain and how often it occurs without there being any peritonitis, to interpret such pain before perforation as due to a local peritonitis hardly seems justifiable, as peritonitis in typhoid fever occurs as the result of perforation in the great majority of cases. Perforation is apparently more likely to occur in patients with diarrhœa. The association of hemorrhage and perforation is not uncommon, as in 10 of the 40 of this series; in 7 they occurred together and in 3 the hemorrhage occurred a few days before. The character of the attack has no marked influence; although in more than half this is severe yet it is not rare to have perforation in a patient with a mild attack.

The onset may be sudden or gradual, a useful classification emphasized by Manges. The diagnosis in the former group can be made much more readily than in the latter, for the mode of onset is one of the greatest aids. In the latter group the symptoms subsequent to perforation are those on which we must depend, but the outlook, even with early diagnosis and operation, is grave in the group with such severe toxæmia that there are few symptoms at onset. In the description of symptoms those given of the onset apply especially to the "acute group." The chances for the early recognition of perforation are greater when the patient is being given the bath treatment, as the mental condition is likely to be clearer and this renders the onset more readily observed and allows a more accurate estimation of the condition.

Onset.—The first symptom in the great majority is the occurrence of sudden, sharp, severe abdominal pain. This was the case in 26 of 32 patients of this series in whom the onset was noted. Of the others, in 6 there was no note, in 2 the time of onset was doubtful, in 2 the patient was delirious and there was no complaint of pain, in 2 the patient was admitted with general peritonitis and gave no history, in 2 the perforation occurred just before death from toxæmia. In some patients dying from toxæmia, perforation may occur while the patient is moribund. In these there may be no symptoms and a diagnosis is impossible; operation is out of the question,

and the condition can be recognized only at autopsy. In some of these the perforation may be found with little or no resulting peritonitis.

The mode of onset is the most important point in the recognition. If the patient is seen then, it may be possible to make a diagnosis with reasonable certainty, which later on can be made only with great difficulty. The pain is usually paroxysmal and rarely constant. Between the attacks the patient may be fairly comfortable and show no definite signs, so that it is important to sit down by the bedside and watch for some time. That one may do this intelligently it is important that the previous condition should be accurately known. As a rule the pain returns before a very long interval but may last only for a short time. The seat of the pain of onset varies considerably but is usually in the lower abdomen, sometimes about the navel or in the right iliac fossa. In males it may be referred to the penis. With the pain the patient may complain of bladder irritability with frequent micturition. On examination one may find no special change in the appearance of the abdomen. The respiratory movements may be slightly diminished but this is not common. On palpation there is usually marked tenderness, sometimes over the whole abdomen, sometimes localized. There may be some rigidity and possibly muscle spasm but as a rule shortly after perforation these are not persistent and may be present only during the attacks of pain. With the local abdominal features there may be general disturbance, such as a marked change in expression, sometimes associated with sweating or a chill. In some instances there is nausea or vomiting. These are all usually temporary if they appear at the time of perforation. There may be an increase in the respiration and pulse rate. The fall in temperature, so often described, has not been common at the time of perforation in this series. There is more often slight elevation for two or three hours following the perforation and then a fall. It must be said, however, that beyond the pain there may be very little change for an hour or two after perforation.

With suspicious signs, careful notes should be made at once of the general symptoms and the local conditions. Of these the most important are the degree of distension, the extent of the respiratory movements, the amount of tenderness and the presence of rigidity or of muscle spasm. With this there should be hourly records of the temperature, pulse and respiration, with the blood pressure taken every fifteen minutes. All this represents much work, but it must be recognized that if we are to make an early diagnosis of perforation we must be prepared to devote every energy toward it.

In the few hours after perforation there may be little change. The pain may recur at intervals, generally paroxysmal in character, but otherwise there is little alteration. The principal features can perhaps best be discussed separately.

1. *General Appearance.*—This may be suggestive at the onset, the features having a more or less pinched expression especially if there be sweating. As a rule this does not persist and in a few hours later there may be nothing marked. If general peritonitis develops we have the characteristic facies of that condition.

2. *Temperature.*—The course of this is variable. In many patients immediately following perforation there is a slight elevation followed later by a drop. There is no rule regarding this and a sudden fall or sudden elevation may occur with the perforation. Later on the temperature may

rise with the peritonitis, but as a rule changes in the temperature are too uncertain to be of much value.

3. *Pulse and Respiration.*—Usually these both show increase but there is no certainty in this, for patients have been operated on in whom neither the pulse nor the respiration rates had especially altered. Generally the respiration rate increases at the time of perforation and this may be a valuable sign. Later on both the pulse and respiration rate almost invariably increase.

4. *Gastric Symptoms.*—Hiccough, nausea or vomiting may occur at the time of perforation. These are always suggestive signs and may draw attention to the complication. In several patients, the sudden occurrence of one of these has first aroused suspicions of perforation. They are especially important because so rare in typhoid fever.

5. *Abdominal Conditions.*—These are by far the most important because while other things may rouse suspicions, it is by the abdominal signs that the diagnosis is usually made. Abdominal pain may be fairly constant but is usually paroxysmal. The local abdominal features are (*a*) increase in distension, which is often not present until some hours after perforation. It should always be carefully looked for, as increasing distension is a most important point. (*b*) Changes in the respiratory movement: These if present early are very valuable. The decrease in the extent of movement may be seen only below the navel or may be more on one side than the other. But general peritonitis may be present with well-marked retention of the respiratory movement. (*c*) Rigidity: This is a most important condition and should always be most carefully noted. Light palpation should be employed and it is especially important to compare the two sides of the abdomen. With perforation it may be some hours before rigidity is marked and too much importance should not be attached to its absence. Persistent rigidity of one rectus muscle is an important sign. (*d*) Muscle spasm: This is as a rule the most important local sign. It may be quite local and found in part of one rectus only. (*e*) Movable dulness: This may suggest the presence of free fluid in the peritoneal cavity but great caution should be observed in drawing such a conclusion, as it may be given by fluid in the bowel. This is especially likely to occur if there has been diarrhœa, which is often the case in the patients with perforation. (*f*) Obliteration of liver dulness: This is of value in two conditions; first, if it occur in an abdomen which is flat or scaphoid, and second, if it has appeared suddenly in a non-distended abdomen. If there be any degree of distension no dependence should be placed on it. (*g*) Signs on auscultation: These are of very doubtful help. Some writers, especially the French, have laid stress on the fact that gas could be heard escaping from the bowel through the perforation. The writer heard it in one patient with perforation in whom there was also a curious sound on auscultatory percussion comparable to the coin sound in pneumothorax.

6. *Rectal Examination.*—This should always be made, although it rarely gives information of value. If the process be low in the abdomen there may be marked tenderness on pressure high up in the rectum, sometimes more on one side than the other.

7. *Bowels.*—As a rule they do not move after perforation but this is not invariable and in cases of this series both flatus and fæces have been passed.

8. *Leukocytes.*—Perforation is usually followed by an increase in their number. There are three fairly well-marked groups of cases: the first in which there is a steady increase in the number from hour to hour; the second in which there is a slight increase in the first two or three hours and then a rapid fall, and the third in which there is practically no change or even a fall. The initial rise may be very temporary and disappear in three hours. It is evident that counts can be of service only if there are previous ones available for comparison. Many of the conditions which cause abdominal pain may also produce leukocytosis. It is in the group in which the leukocytes increase steadily that the blood counts give the most assistance. The presence of leukocytosis is most important but from its absence no conclusion should be drawn. A steadily dropping count may suggest a severe general peritonitis.

9. *Blood Pressure.*—In many patients there is a sharp rise with the perforation. This is not invariable, as in a recent case the blood pressure did not show the slightest change. Probably any condition causing pain may produce a rise in the blood pressure. It should be of aid in the diagnosis of hemorrhage from perforation. In one patient the rise in blood pressure occurred about three hours before the first sign of perforation.

Advance in the signs is an important aid and the patient should be carefully watched for this. The distension may gradually increase, the respiratory movements decrease and the tenderness with rigidity and muscle spasm become more marked. But one should not wait for too much advance before deciding on exploration.

Lastly, as an aid in the diagnosis of perforation we must include an exploratory incision, for it is well to recognize that it may be impossible to make a positive diagnosis without this. The important matter to decide is whether there exists an abdominal condition which justifies exploration rather than to make a positive diagnosis of perforation. An acute abdominal complication is what we have to recognize—this is perforation in the majority. In some patients, especially those who are toxic or delirious, it may be quite impossible to make an early positive diagnosis. No one can lay down rules which will always apply—every patient is a new problem. The conditions which are most likely to be mistaken for perforation are as follows:

1. Peritonitis from other causes: This is not common and its definite recognition is difficult. In one patient at operation a beginning peritonitis was found for which no cause was discovered. Fortunately in these cases an exact diagnosis is not an important matter because the treatment is the same as for perforation. 2. Appendicitis: This may be due to a typhoid process or may be distinct and either acute or acute exacerbation of a chronic condition. The condition can hardly be positively recognized and the same remarks apply as to the preceding group. 3. Hemorrhage: This may give a picture much like perforation but the fall in blood pressure and in the percentage of hæmoglobin is an aid in diagnosis. The association of the conditions has to be kept in mind and every patient with hemorrhage should be carefully examined with the possibility of perforation in view. Rigidity and muscle spasm are not as common in hemorrhage as in perforation. In one patient of this series with both, in whom the symptoms were very severe, the fall in hæmoglobin did not seem enough to correspond to a hemorrhage sufficient to give all the symptoms. The difficulty of diagnosis when the two conditions are present is very great. 4. Phlebitis: This in the iliac veins may give very suspicious symptoms and in one such case of this series

exploration was done. The careful examination of the leg for swelling and the femoral region for tenderness may give the correct diagnosis. 5. Intestinal conditions, such as obstruction, strangulation, intussusception, may cause difficulty. 6. Attacks of abdominal pain without evident cause: In these patients careful continued examination is the greatest help. The abdominal signs do not usually show the advance which we often find in the perforation cases. 7. All the conditions which have been noted as causing abdominal pain may give difficulty but a careful routine examination should exclude them beyond doubt. Perforation of an ulcer in the stomach does not require any special discussion.

The possibility of recovery without operation, after perforation of the bowel, is an interesting question but it is doubtful if practically it is worthy of much consideration. The omentum or adhesions may very rarely close the opening. Certainly it should never be used as an argument against operation. There can be no question of its occurrence but the estimates given by some writers do not seem to be supported by any records. A diagnosis of perforation made without operation or autopsy is open to great doubt. Some patients with suspicious symptoms are operated on and no perforation found, while others may show symptoms which are very suggestive but, dying later of other conditions, the peritoneum is found perfectly clear at autopsy. In rare instances a local abscess may follow perforation. This may be drained subsequently or rupture internally exactly as an appendix abscess. In a recent case, there was empyema and septicæmia secondary to such an abscess.

General Peritonitis.—The characteristic general expression, the pulse small and running, the temperature variable, sometimes being high but in others low, require no comment. There may be hiccough with nausea and vomiting and but little complaint of spontaneous pain. The abdomen is usually distended, although there may be general peritonitis with a scaphoid abdomen; the respiratory movements are diminished or absent; there is usually tenderness with marked rigidity and perhaps muscle spasm. It can not be emphasized too strongly that the symptoms of perforation are quite distinct in the majority of instances from those of the resulting general peritonitis. With the latter condition present the chances are always much in favor of its being due to perforation.

Peritonitis from Other Causes than Perforation.—The frequency of this is difficult to estimate. Some writers put it as high as 1 per cent. or even more. The subject has been carefully studied by Yates.[1] In this series there were four instances, one from a simple appendicitis, one from old pelvic disease, one from ulcer in the gall bladder without rupture, and one without discoverable cause. The principal causes are as follows: (*a*) Extension from the ulcers. It is difficult to say how often this occurs but it is probably not common. In 2 of this series at autopsy there was a thin fibrinous exudate over the areas of intense injection corresponding to the ulcers. Various organisms may be obtained from these areas and it seems reasonable to suppose that a peritonitis may be set up in this way, the organisms passing from the mucosa to the serosa. This may be more or less localized and it is quite possible that some of the instances which are regarded as recovery from perforation belong to this group. In the same way a local peritonitis

[1] *American Medicine*, vol. v, 1903, p. 700.

may arise from extension from an ulcer in the gall bladder, as in one of this series. (*b*) From suppurative processes. This is rare but such instances are on record. These possible sources are various, and include rupture of a suppurating mesenteric gland, rupture of an abscess or infarct of the spleen, abscess of the liver, abscess of the abdominal wall, abscess about the bladder, and thrombosis. (*c*) From pelvic conditions. An ovarian abscess, disease in the tube or an infective process in the uterus may be the source. (*d*) Other intestinal conditions such as appendicitis apart from a typhoid lesion or strangulated hernia. (*e*) Without any evident cause. It is possible that this may be from the passage of bacteria through the intestine or from a periadenitis.

The reported cases studied by Yates showed the time of greatest incidence about the end of the third week. It occurred both in severe and mild attacks and with slight and deep ulceration. In the majority the onset was acute and as a rule the diagnosis of a perforation was made. Abdominal pain was the most constant symptom and was usually on the right side. Rigidity was usually found at some time. The temperature curve was variable. Of 11 patients operated on, 4 recovered; and of 9 not operated on, all died. The type of peritonitis varied from serofibrinous to fibrinopurulent. In the majority it is not possible to distinguish the condition from perforation before opening the abdomen.

Conditions of the Rectum.—Ulceration occurs in a moderate number of cases and there is danger of perforating the ulcers by the tube in the giving of irrigations or enemata. They may account for some of the instances of slight hemorrhage after enemata. Perforation of an ulcer in the rectum may occur, as in one of this series, usually with the production of an abscess. Unless complaint is made by the patient, recognition will be difficult. Local examination will probably be the greatest aid.

The Spleen.—While enlargement of the spleen is common in infectious diseases generally, yet in none has it the same importance as in typhoid fever The recognition of splenic enlargement is most certain by palpation. Percussion is of value in determining increase in size, especially when the spleen cannot be felt, but distension of the colon and stomach may interfere greatly with this. There are certain conditions which prevent the spleen being palpated even when it is much enlarged; thus if the thorax be very deep, only an enormously enlarged spleen could possibly come near the costal margin. In patients who have very thick abdominal walls or in whom there is much distension or tenderness, the spleen may not be felt. It is doubtful whether previous conditions, such as adhesions, affect the enlargement very materially.

Enlargement as a rule is greatest at the height of the attack, although the spleen may be palpable very early. In some patients it may first be felt when marked emaciation has rendered palpation easier. There may be a marked reduction in size after intestinal hemorrhage. As a rule the spleen diminishes in size in the latter part of the attack, although in some patients the enlargement may continue after the temperature is normal. It is safe to consider these as in greater danger of a relapse. If the spleen has become much reduced in size after the original attack, the enlargement may return with a relapse but rarely with a recrudescence. In some instances the spleen is felt for the first time in the relapse. The spleen was felt in 1,075 of the 1,500 cases (71.6 per cent.).

The spleen in typhoid fever is usually soft, although in patients who have had malarial fever it may be quite hard. As a rule it is not painful, although some patients complain of tenderness on palpation. In some there is complaint of pain in the left costal region which may be persistent and not made markedly worse by palpation. In such cases the occurrence of perisplenitis may be suspected and this diagnasis may be made if the pain be severe and rendered more so by deep breathing, pleurisy being excluded. Other conditions of the spleen such as spontaneous rupture, infarct, abscess, etc., are rare but are sometimes possible of diagnosis.

The cause of the enlargement is difficult to give. It probably stands in relation to the involvement of the lymphoid tissues generally, the toxins probably the causal agents. The increase in size bears no definite relation to the severity of the attack for a much enlarged spleen may be found with mild symptoms.

Liver.—This organ plays little part in an ordinary attack and subjective symptoms referred to it are rare. There may be complaint of pain in the liver region with tenderness and perhaps slight enlargement. The common focal necroses in the liver do not give any clinical symptoms so far as we know, although in some they may be associated with jaundice. The most important liver conditions which occur are jaundice, abscess, suppurative pylephlebitis and cholangitis.

1. *Jaundice.*—This may occur as catarrhal jaundice, toxic jaundice or with abscess and cholecystitis. It is rare and, apart from abscesses and cholecystitis, was present in 8 patients in this series. The co-existence of gall stones may be a cause. (*a*) Catarrhal jaundice: This is usually of a mild grade and seldom causes any severe symptoms. It is rare at the beginning but may occur at the height of the attack or in the latter part of the course. The most probable explanation is that typhoid bacilli in the ducts set up a mild grade of inflammation. It may be quite possible to distinguish between a catarrhal and a toxic jaundice. The occurrence in milder attacks and the absence of bile in the stools are in favor of the catarrhal form. (*b*) Toxic jaundice: This is more likely to occur in severe attacks and late in the course. Bile is usually present in the stools. In some instances a condition much like acute yellow atrophy has been described, associated with a rapid course with jaundice, marked decrease in the size of the liver, hemorrhages and a termination in coma.

2. *Abscess.*—This is a rare complication and was present in only two of this series during the attack, while in a third patient an amœbic abscess developed during convalescence. The abscess may be single or multiple, the latter usually occurring as part of a general septic process and perhaps associated with parotitis, perichondritis, etc. In others it may be secondary to infection in the abdomen, such as mesenteric abscess or pylephlebitis. Multiple abscesses have occurred after cholecystitis. The causal organism is the typhoid bacillus in a few instances, the colon bacillus, or pyogenic cocci.

The symptoms are pain in the region of the liver, increase in its size, jaundice, marked leukocytosis and possibly the muddy color of the skin sometimes associated with abscess. Pus may be obtained by exploratory puncture. The conditions from which abscess has to be diagnosed are cholecystitis, subphrenic abscess and empyema. A liver abscess in typhoid fever may be latent and, as in one of our patients, discovered only at autopsy.

3. *Suppurative Pylephlebitis.*—This is very rare and is usually associated with thrombosis of the portal veins. Osler has reported a case associated with mesenteric abscess.

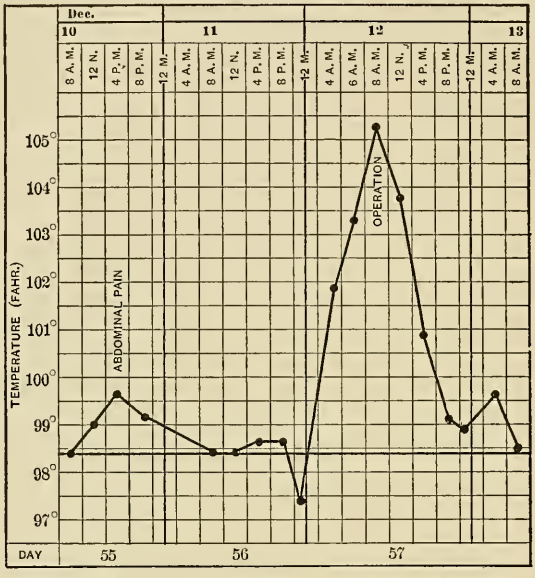
Gall Bladder.—The relations of typhoid bacilli to the gall bladder are as follows: (*a*) In the great majority, perhaps always, typhoid bacilli are present in the gall bladder during the attack. (*b*) The bacilli may persist in the gall bladder after an attack for an indefinite period, instances of fourteen, seventeen and eighteen years being on record. (*c*) Typhoid bacilli may occur in the gall bladder as a local infection without the patient ever having had typhoid fever. Pratt has collected 5 such cases.

During an attack the typhoid bacilli probably reach the gall bladder through the blood. They may be excreted from the liver or gain access through the ducts but this latter method does not seem probable. In the majority no symptoms are set up, and with cholecystitis it may be difficult to assign any reason for the complication beyond the presence of the bacilli. In a certain number, the determining factor is the presence of gall stones but this is not common during the attack, being found only in 4 out of 115 cases collected by Camac, although it has been suggested that the formation of gall stones may be very rapid. The organisms may be found in clumps in the gall bladder. Secondary infection with other organisms is rare. Obstruction to the flow of bile undoubtedly favors the development of cholecystitis which in some grade is probably much more common than is usually supposed, as only the more severe attacks are noted. The diagnosis was made in 19 of this series (1.2 per cent.). The extent of the process may be very variable. There are probably all stages from a simple catarrhal cholecystitis to ulceration and perforation. In rare cases with ulceration there may be extension and a local peritonitis set up without any perforation of the gall bladder. The time of the occurrence of cholecystitis varies greatly, the earliest in this series being on the eighth day and the latest on the fiftieth day. It may appear at the height of the attack or after the temperature is normal and it may be difficult to say whether it should be regarded as a complication or a sequel. The majority occur during the third week or later, sometimes with a relapse.

The onset is usually sudden with pain in the region of the gall bladder. There may be a chill or vomiting. The pain usually persists and may be situated close to the costal margin or lower down on the right side. On palpation there is usually marked tenderness over the right side of the abdomen, especially in the upper quadrant and with this probably rigidity and muscle spasm. In the febrile cases there may be an increase in the temperature or a sudden rise if the temperature has become normal as shown in Figs. 10 and 11. The pulse rate usually increases and in some the respiration also. There may be diminished respiratory movement both of the thorax and abdomen on the right side. Vomiting or a chill may occur after the onset. Jaundice may follow and was present in 6 among 19 cases. There is usually leukocytosis, generally from 10,000 to 15,000, rarely reaching 20,000. The gall bladder is sometimes felt. The progress of the condition is very variable. It may persist for a few days, usually four to eight, and then disappear or go on to perforation. The symptoms of perforation require no special discussion but it has to be remembered that when a patient has been having abdominal pain from cholecystitis for some days there may not be change enough to suggest a perforation before the onset of general

peritonitis. Perforation may happen in a gall bladder which is not palpable and not especially enlarged. General peritonitis usually follows perforation; there are rare instances of the process being localized. In very toxic patients,

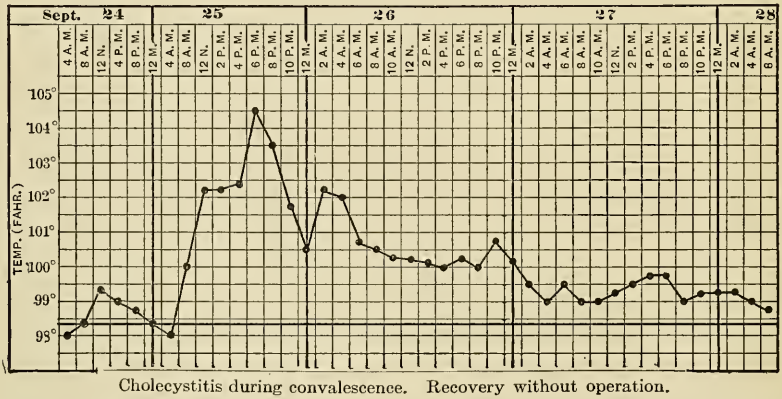
Fig. 10.



Cholecystitis during convalescence. Operation. Recovery.

perforation and general peritonitis may be present before the condition is recognized. The patient should be watched most carefully and frequent records made just as in the case of suspected intestinal perforation. It is

Fig. 11.



Cholecystitis during convalescence. Recovery without operation.

well to have a surgeon see the doubtful cases early. Tapping the gall bladder in such a condition is not justifiable either for diagnosis or treatment. Perforation of the gall bladder and intestine have occurred together.

In some instances, cholecystitis may seem to be more a sequel than a complication. There can be no doubt of the influence of typhoid fever on the formation of gall stones. Typhoid bacilli may be found in the gall bladder without any previous attack of typhoid fever so far as known. The possibility of a mild attack which has not been recognized has always to be remembered.

Pancreas.—Hemorrhagic pancreatitis is very rare but has occurred.

The Respiratory System.—The Nose.—Early in the disease there may be hyperæmia of the nasal mucous membrane, although coryza is rare. This may result in the passage of a little bloody mucus but frequently there is definite bleeding. Epistaxis occurs quite frequently during the incubation and also in the early febrile stage. It may occur during the course or even in convalescence. It is much more common at the beginning of typhoid fever than any other acute infection and occurred at onset in 323 of this series (21.5 per cent.). As a rule, the bleeding is rarely profuse, but it may prove alarming and a few cases are on record (apart from the hemorrhagic type) in which death resulted directly from the epistaxis. It may be necessary to plug the posterior nares. As a rule nose bleed occurs most frequently in children and young adults. In the hemorrhagic type it may be very severe.

The Larynx.—Serious involvement is recognized in a comparatively small number of cases. In patients who are very ill and breathe through the mouth, both the pharynx and larynx show a condition which may be termed a "dry catarrh." A simple catarrhal inflammation may be present but ulceration of the mucous membrane is more serious. This was found in 3 cases of this series at autopsy, in one associated with necrosis of cartilage. Jackson has divided the lesions into: (1) subacute laryngitis, (2) ulcerative laryngitis and (3) perichondritis. The first was found in 237, the second in 68, and the third in 17, of 360 cases. Ulceration occurred usually after the third week, the average being the thirty-first day, and in patients with severe infection. Two-thirds of his patients recovered perfectly. Curschmann considers that the ulcers have two modes of origin. Necrosis follows the swelling of the lymph follicles and in some of these cases typhoid bacilli have been obtained in cultures or the ulcers follow fissures and erosions, usually on the posterior part of the larynx or along the border of the epiglottis. These lesions once begun, tend to increase rapidly in severe cases. As a result of increase in the process there may be extension to the cartilages or infection of the surrounding tissues. There may be perichondritis or the cartilages may be almost entirely destroyed; the process may be primary in the cartilage. One patient of this series coughed up both arytenoid cartilages. In some instances the changes in the larynx have resulted in stenosis. Œdema of the glottis occurs, as was found in 2 of this series at autopsy; ulceration of the epiglottis was found in 1.

The laryngeal complications are often overlooked during life. When they occur in patients who are very toxic, no complaint is made and examination of the larynx is often difficult. There may be dyspnœa, hoarseness and cough, or even loss of voice. The patient may complain of pain and probably have difficulty in swallowing with pain on pressure over the larynx. The danger of acute œdema of the glottis makes it necessary to watch these patients very carefully. Paralysis of the laryngeal muscles occurs rarely and is probably due to neuritis. Some of the older writers describe diph-

theritic affections of the air passages, but probably many of these were associated with ulceration and the deposit of a large amount of mucus.

Respiration.—The respiration rate is often somewhat increased, perhaps to 24 or 28 per minute, even when no complication is present. Dyspnœa is rare.

Bronchitis.—This is one of the early symptoms although the patients rarely make any special complaint of it. Usually regarded as almost a specific symptom, the bronchitis shows no special peculiarities. The cough is frequently harsh, with scanty and rather tenacious sputum, occasionally containing small amounts of blood. The principal physical sign is the presence of numerous rales. In some instances the cough is unusually severe and slight cyanosis is present which is usually taken to indicate especial involvement of the smaller tubes. The severity of the bronchitis does not necessarily bear any relation to the character of the attack, as mild infections may show severe bronchitis. As a rule it lessens in the second week and often disappears very rapidly but in some patients it may prove troublesome throughout or return during the latter part of the attack. Occasionally collapse of the lung or bronchopneumonia may follow. The occurrence of typhoid bacilli in the sputum is a point to which attention should be given. Bronchitis does not appear to be of importance in the fatal cases and was noted only in 4 of 105 autopsies, in 2 of which it was described as putrid bronchitis.

Lobar Pneumonia.—The figures in the literature as to its frequency are variable, some considering that it occurs in 10 per cent. of all cases. This does not agree with this series, as lobar pneumonia was found in only 22 cases (1.5 per cent.). It occurred in 233 of 8,356 cases in the London Fever Hospitals (2.7 per cent.). It is convenient to separate two conditions under which it occurs. (1) At onset: This is termed pneumotyphoid by French and German writers and occurred in 3 of this series. The attack begins with the usual features of lobar pneumonia, chill, pain in the side, fever and characteristic signs in the lung. The attack may run the course of an ordinary lobar pneumonia without a suspicion of anything else being entertained and only the persistence of the fever suggests another condition. There may be a termination by crisis, the temperature falling to normal for a day and then rising again. It may be difficult to say whether we have an ordinary lobar pneumonia followed by typhoid fever or typhoid fever with early involvement of the lung. In one patient in whom there were no intestinal lesions there was consolidation of one lung, associated with gangrene, the organism present being the typhoid bacillus. (2) It may occur during the course, as in 19 of this series, and is most frequent during the second and third week. The symptoms may be few in number, the patient not making any complaint of pain or distress, especially if the mental condition be dull, and only an increase in the respiration rate with cyanosis may draw attention to the condition. Leukocytosis may not be present. The sputum may be slight in amount or swallowed but in some instances has the characteristic rusty appearance. In all severe attacks a routine examination of the lungs should be made every day, for it is only by doing this that some of the cases will be recognized early. Curschmann thinks that a certain number do not go beyond the stage of congestion, as was found in 2 fatal cases of this series. Lobar pneumonia was found at autopsy in only 6, a rather small percentage, and in 1 was associated with gangrene.

There is another condition of the lungs which is difficult to classify. It resembles an atypical lobar pneumonia and may come on at the onset or during the course. There may be complaint of pain in the side and possibly slight cough. The sputum is usually scanty but not rusty or bloody. Physical examination shows restricted movement on the affected side, vocal fremitus usually somewhat increased, marked dulness on percussion, and variable signs on auscultation. The breath sounds may be harsh and accompanied by a few fine rales at the end of inspiration but are not typically tubular. In others they may have a tubular quality during only one part of respiration, or they may be feeble with a very distant tubular quality. This condition is more frequent on the right side. It rarely involves the whole of the lobe and the most marked feature is its irregularity. The course is very variable; in some it persists for perhaps only three or four days and then clears gradually, in others the dulness may persist well through the attack of fever and then clear entirely so that in convalescence the lung is perfectly clear. In some of these cases the diagnosis of pleurisy may be suggested, but the absence of a friction rub, the usual increase in the vocal fremitus, and the character of the breath sounds, are against this. It seems best to consider them as examples of atypical lobar pneumonia. The association with typhoid fever is not uncommon. It does not appear to be a serious condition and there has not been any opportunity to examine the lung at autopsy.

Bronchopneumonia.—This is usually a terminal event. In 8,356 cases from the London Fever Hospitals it was found in 1.2 per cent. It was found at autopsy in 37 of this series (35 per cent.). In some it is due to the typhoid bacillus but in the majority pyogenic organisms are found. Coming on, as a rule, when the patients are very ill, it may not give rise to any marked symptoms. The onset may be with a chill. The increase in the respiration rate, cyanosis and perhaps some slight physical signs may give the diagnosis. Œdema, abscess or infarction may be associated. In some cases there may be an aspiration pneumonia, which is especially likely to occur in patients who are very dull. In patients with ulceration in the larynx there is always great danger of secondary pneumonia.

Hypostatic Congestion and Pneumonia —These are especially likely to occur in patients with long, severe attacks. If they appear early it is of serious import, although as a rule their occurrence is late and favored by cardiac weakness and the position of the body. This latter is of great importance and the endeavor should be made in all severe attacks to keep the patient turned on one side or the other and off the back as much as possible. But by far the most important preventive of hypostatic pneumonia is the bath treatment. It was found in only 2 of this series at autopsy. It may not give rise to any symptoms and will rarely be recognized unless regular routine examination of the thorax is made. As a rule, there is defective resonance at the base, the note having a slight tympanitic quality. The vocal fremitus is often difficult to obtain. It may be diminished if the bronchi are full of mucus or the voice very feeble, but otherwise is somewhat increased. The breath sounds are usually feeble and as a rule there are numerous moist rales. Such a condition may be associated with bronchopneumonia or œdema. It may be difficult in some cases to estimate just how much consolidation is present. Hypostatic pneumonia is an exceedingly dangerous condition and, if well established, recovery rarely occurs.

There are other lung complications which occur occasionally. Infarction, which was found in 4 of this series at autopsy, offers no special features. Infarction or pulmonary embolism is rare as a result of detachment of the clot in thrombosis. Abscess of the lung is infrequent and may be associated with pneumonia or general septic infection. It was found in 4 of this series at autopsy in association with bronchopneumonia. Gangrene of the lung is also rare, and as a rule occurs late in the attack. It was found at autopsy in 2 cases, in one with thrombosis. It may occur under the same condition as aspiration pneumonia and in some instances has been apparently due to the presence of particles of food in the lung.

Hæmoptysis.—This may occur in the hemorrhaigc type as part of the process. In a few patients small amounts of blood are brought up, most of these being probably due to an intense bronchitis. It may be due to an associated pulmonary tuberculosis. It is possible that some are due to small hemorrhagic infarctions.

Pleurisy.—This is not very common, having been noted in 32 of this series (2.1 per cent). It was found at autopsy in 9 cases. Pleurisy may be common in some epidemics. Thus Heymann[1] reports 17 cases in a series of 129 (13.8 per cent.) in Würzburg, only one of which was associated with a lung condition (pneumonia). It was present in 92 of 8,356 cases in the London Fever Hospitals (1.1 per cent.). Pleurisy may occur at the onset or more frequently during the course. Instances of the former in which the pleurisy is a prominent feature are termed pleurotyphoid by the French. The onset may be sudden with high fever, severe pain in the side, and a well-marked friction rub. The majority of this series have been of the fibrinous type and in only four was there effusion. This may be serous or purulent, there having been three of the former in this series and one of the latter from which typhoid bacilli were obtained. The purulent type is most often seen during convalescence. In many instances pleurisy is secondary to conditions in the lung, such as pneumonia, infarct and gangrene. Hemorrhagic effusions have been noted and there is the possibility that a tuberculous pleurisy may co-exist with typhoid fever. In Heymann's cases there was effusion in 10—in 1 hemorrhagic and in 1 purulent; in 2 the typhoid bacillus was obtained; death occurred in 4 out of the 17 cases.

The question of the organism concerned in the lesions of the respiratory tract is an interesting one. The ulcerative processes about the larynx are apparently due in the majority to the pyogenic cocci but in a small number typhoid bacilli have been obtained. In the lung the determination of the causal organism may be difficult. The typhoid bacillus is probably present in the lungs in every case and can frequently be obtained by puncture. However, the examples of lobar pneumonia due to the typhoid bacillus alone are exceedingly few. The cases reported by Flexner and Harris, and Robinson, seem definitely established. In the majority the pneumococcus is present, and may be associated with the typhoid bacillus. That the typhoid bacillus alone may be responsible is supported by the fact that in one case of lobar pneumonia a paratyphoid organism was obtained in pure culture. It seems fair to hold that while in the majority of cases lobar pneumonia is due to the pneumococcus, with which the typhoid bacillus is often associated, yet in rare cases the typhoid or paratyphoid bacillus is the causal organism.

[1] *Inaugural Dissertation*, Würzburg, 1904.

It has been suggested that pulmonary typhoid lesions are likely to be hemorrhagic, but there is hardly a sufficient number of these cases to justify this conclusion. In bronchopneumonia the typhoid bacillus is probably present more frequently than in lobar pneumonia. Among 14 cases with satisfactory cultures, the typhoid bacillus was obtained in pure culture in 2, both the colon and typhoid bacillus in 2, colon and typhoid bacillus with staphylococcus in 1, pneumococcus in 1, pneumococcus and colon bacillus in 2, pneumococcus, colon bacillus and staphylococcus in 2, streptococcus in 2, and staphylococcus and bacillus proteus in 1 each. In the cases of gangrene and abscess the typhoid bacillus may be obtained in pure culture. The same is true in pleural effusion, and the typhoid bacillus in pure culture has been obtained from both the serous and purulent exudate. The sputum of the patients with pneumonia often contains typhoid bacilli.

The Circulatory System.—The conditions in the patients of this series have been especially studied by Thayer. As a rule the state of the circulation is an important indication of the condition. A variable degree of capillary stasis is common and may be extreme, especially over the back, but does not seem to be of any special moment. The pulse in typhoid fever may not give any characteristic findings. As a rule during the early stages, the increase in the rate is less than would be expected from the fever. This may be true of some patients all through the attack, the rate never reaching 100. Thus, among the last 500 cases in the series there were 176 in which the pulse rate was not above 100, in 60 not over 90, and in 21 the rate was not over 80.

Dicrotism.—There is no disease in which a dicrotic pulse occurs so frequently. It may be marked early in the course and continue throughout. It is probably due to the reduction of the tension of the arterial wall. In rare cases the pulse may show several secondary waves. The dicrotic pulse is generally most marked in adults; in children it may be present but as a rule is not marked. In patients with arteriosclerosis it may be absent.

Rate.—At the height of the disease the pulse may show marked variation. It may become very rapid, 140 or over, and then it is usually small and running. These patients as a rule are seriously ill and the prognosis is always grave. The pulse rate may show a marked response to any nervous influence. This is especially evident in hospitals on visiting days when the pulse rate of all the typhoid patients may show a definite increase which is usually persistent for some hours.

A sudden increase in the rate should always suggest careful search for a possible complication. With the onset of pneumonia the rate may rise but it is especially important with abdominal complications, notably hemorrhage and peritonitis. Hemorrhage of any amount usually causes marked increase and this may suggest bleeding before any blood has been passed. There is sometimes a marked change in the pulse about the time of a hemorrhage. This consists in a curious bounding quality which is rarely observed under any other circumstances. With perforation and peritonitis there is some increase in the majority of cases. In very severe attacks toward the end the pulse may become so rapid and running that it can hardly be counted. The records of this series show that in 223, or 15 per cent., the pulse rate rose above 140. Of these, 46 were under fifteen years of age, and of the remaining 177 patients 86, or 48.5 per cent., died. In 77 patients the pulse rate rose above 150 and 55 of these, or 71.4 per cent., died. In 51 patients the rate rose above 160 and of these 35, or 68.5 per cent., died. In 6 the rate

rose above 170 and of these 4 died. In 2 a rate of over 180 was noted and 1 of these died. Death followed in both instances where the pulse could not be counted. Irregularity is not very common but, if present with a rapid rate, is of serious import, and of 13 patients with a pulse rate above 140, associated with irregularity, 9 died.

The tub baths make a considerable change in the quality of the pulse. While in the tub the pulse usually becomes small and there may be difficulty in feeling it at the wrist. This continues for some time and as the interval from the tub increases the pulse becomes softer and more flabby. The character of the pulse immediately before is in marked contrast to that after the bath. The one is soft, flabby, easily compressed and relaxed, if one may use the term, while the other is usually firm and hard.

During convalescence the pulse rate gradually drops and may show remarkable variations. Any little exertion or excitement may increase the rate from 20 to 50 beats a minute as seen in some patients about the time they begin to get about. This may continue for some weeks and as a rule is not serious, although it should suggest caution in letting patients do very much. Slowness of the pulse may be present during convalescence. This is by no means uncommon and the cases seem to fall into two groups. In one the slowness is not constant but is seen perhaps only during the morning hours of each day, when the rate may be from 40 to 60 and later in the day rises to normal. This may continue off and on throughout convalescence. To such cases the term bradycardia can hardly be applied. In the second group we have the true instances of bradycardia, which is more frequent after typhoid fever than any other acute infection. The pulse may sink to 40 or even 30 beats a minute and is usually small. This slow rate may continue for a considerable time and the return to normal be very gradual. It is perhaps most marked during the period of subnormal temperature so often seen during convalescence. With the bradycardia there may be irregularity or intermittency. In 117 patients a pulse rate below 50 was noted during convalescence. In 6 a rate below 40 was noted, and the lowest, noted in 2, was 35. The fact that all of these patients recovered is significant and justifies the opinion that it is not a serious condition. It is apparently not to be compared in gravity with the bradycardia seen after diphtheria. Irregularity with bradycardia does not seem to be a serious sign.

Heart.—The heart cannot be said to show any changes peculiar to typhoid fever. The variations in the rate, character of the sounds, etc., may be due to several factors such as fever, toxæmia, vasomotor paralysis with a secondary effect on the heart muscle, and myocardial changes. Dilatation may be present but it is not often marked and is more common on the left than on the right side. With the progress of the attack the impulse usually becomes feeble and the apex beat may be diffuse or completely absent.

Heart Sounds.—These may be normal and unchanged throughout, as is seen in mild attacks, but as a rule some change is noted. The first sound usually becomes feebler and may have a muffled uncertain quality which may progress until it becomes inaudible. The second sound may become sharper and more accentuated as the disease progresses. Certain of the descriptions of the heart sounds have come down to us from the days when typhus and typhoid fevers were confused.

In 1,125 cases of this series the heart sounds were clear throughout. In 333 (22 per cent.), murmurs were heard at some time. Of these, 16 were

thought to be due to previous valvular disease and one was associated with exophthalmic goitre. Of the remaining 316 cases, the murmur was systolic in 312, diastolic in 1, and in 3 both systolic and diastolic. Of the cases in which a systolic murmur was heard, the situation was at the apex alone in 87, heard generally in 66, at the apex, tricuspid and pulmonic areas in 49, at the pulmonic area alone in 35, at the aortic and pulmonic areas in 21, at the apex and pulmonic area in 20, and the remainder in various associated areas. Of the 244 cases with a systolic murmur at the apex, this was present on admission in 199. The murmur was observed during the first three weeks in 85 per cent. The murmur persisted through the attack and was present on discharge in 31 out of 138 cases in which the point was carefully noted. The majority of these systolic murmurs were undoubtedly due to relative dilatation of the mitral orifice but it is altogether probable that some were associated with endocarditis.

Endocarditis.—This is one of the very rare complications of the disease. Even large autopsy records give few instances, only 5 per cent. in the Munich statistics. It was present in 6 cases of this series, in 3 of which it was discovered at autopsy and in 3 the diagnosis was made clinically. The mitral, aortic and tricuspid valves have been involved. Instances of malignant endocarditis have been reported. Typhoid bacilli have been obtained from the vegetations and aortic endocarditis has been produced experimentally in rabbits by the intravenous injection of typhoid bacilli. In many of the reported cases other organisms have been found. In the 3 cases of this series staphylococci were obtained. The clinical features are in no way peculiar, but in making the diagnosis of endocarditis the occurrence of a relative insufficiency must be kept in mind as a possible source of error. A leukocytosis would be in favor of endocarditis. Subsequent examination in a doubtful condition should make the diagnosis certain.

Pericarditis.—This is also very rare and was present in 3 cases. In one the patient was admitted on the ninth day with a well-marked rub which persisted for a week, and with this there was a bronchopneumonia. Later there was slight pericardial effusion. In the others, the pericarditis appeared in the fourth week. In the two patients who were conscious there was complaint of severe precordial pain. Death followed in one, and at autopsy typhoid bacilli in pure culture were obtained from the pericardium.

Myocarditis.—To lay down definite rules by which this condition may be recognized is not possible. Rapidity and irregularity of the pulse, gallop-rhythm, embryocardia, a feeble impulse with marked change in the character of the first sound or its becoming almost inaudible, may all be considered as suggestive signs. Yet these may depend on vasomotor paralysis, and the changes in the myocardium occur secondarily. The appearance of a systolic murmur may be regarded as suggestive of myocarditis but may be due to other causes. It is likely to occur during the latter part of the second week and subsequently. The points suggestive of muscular weakness are those noted above, to which a lowering of blood pressure must be added. The changes noted in convalescence, either in the way of marked rapidity or of slowing of the pulse rate, occasional intermittency or irregularity, suggest myocardial changes.

Reference should be made to the instances of sudden collapse which occur at the height or toward the latter part of the attack. Milder grades may occur with some exertion, such as straining at stool, or after mental excite-

ment, but these are rarely serious, of short duration and corrected by stimulation. In another group the collapse appears suddenly and death follows rapidly. The condition of the myocardium or severe vasomotor disturbance may explain some of them. The symptoms are usually those of collapse; the patient looks very ill, the face pale and drawn, dyspnœa and sweating may be present, and with these a pulse which is very rapid and felt with difficulty. Death may follow in a short time, stimulation not being of the slightest use. Such conditions may occur after signs of cardiac weakness or may come on without the slightest warning when the patients apparently are doing well.

Blood Pressure.—The routine record of the blood pressure is of considerable value but this must be taken throughout the attack to be of any help in the estimation of the patient's condition or in the recognition of complications. It may be compared to the pulse rate, which would be of little help to us if we took it only when the condition became serious or complications occurred. As a rule the blood pressure record should be taken twice a day; in severe attacks it had better be taken every four hours, while with the onset of suspicious abdominal symptoms it should be recorded every quarter of an hour while there is any doubt as to the condition. For ordinary work, if systematic records are taken, only the systolic pressure is necessary. The ordinary systolic pressure (Riva Rocci instrument) early in the disease varies from 115 to 125 mm. Hg. There is usually a gradual fall during the course until at the end of the febrile period the pressure averages 100 to 110 mm. Hg. Two or three weeks after the beginning of apyrexia the pressure has usually returned to normal.

Arteries.—Acute complications in the arterial system during the course are uncommon but, as Thayer has shown, conditions may be set up which lead to the development of a considerable grade of sclerosis. Of the acute conditions aortitis has been described but is probably rare. There was no instance in this series. Fresh atheroma is not uncommon, but gives no clinical symptoms. The most important condition is arteritis, which occurred in 4 patients of this series—in 1 in the middle cerebral, in 2 in the femoral, and in 1 in the brachial artery. It is probably due to a localization of the typhoid bacilli or of some other organism in the wall of the vessel. It is a matter of doubt as to whether or not we have arterial thrombosis without a previous arteritis, but the evidence at present suggests that this is rare.

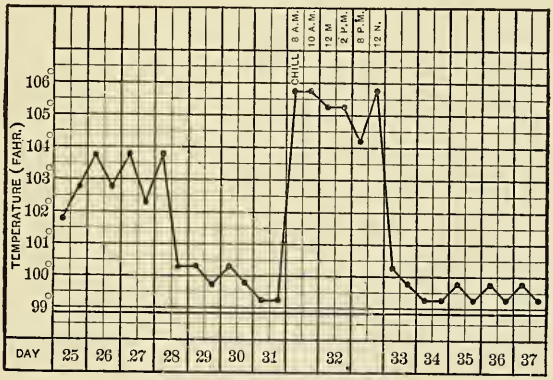
The symptoms of arterial thrombosis usually appear late in the disease. If in one of the vessels of the extremities, the first complaint is usually sudden severe pain along the course of the artery. With this, marked local pain and tenderness are associated; redness and swelling, with perhaps slight increase in the size of the limb, usually follow but as a rule with little or no œdema. Soon there is marked diminution or disappearance of the pulse in the artery peripherally; the extremity becomes cold, bluish in color, and the surface may be somewhat mottled. Following this, one of two things may happen. (*a*) The condition gradually shows improvement; the pulsation returns; the extremity regains its natural temperature and color and is practically restored to normal. Recovery is probably due to the collateral circulation, although channels may be formed through the thrombus. In some there is slightly less pulsation and some slight disability in the affected extremity. Unfortunately this favorable result is not the rule, and we are more likely to have (*b*) the development of dry gangrene. This is usually ushered in by

an increase in the coldness and discoloration of the limb. The gangrene may affect only the peripheral parts or may extend up to the site of the thrombus.

The above description applies to the cases where arterial thrombosis occurs in the vessels of the extremities. When in the cerebral vessels, coma and convulsions with a sudden termination may follow. It may be that some of the instances of aphasia and hemiplegia are due to this complication Whether in the cerebral vessels or in those of the extremities it is exceedingly serious. Minute emboli may occur in the kidneys and spleen, but as a rule give no distinctive symptoms. Embolism of the pulmonary artery may be a cause of sudden death.

Veins.—Complications occur in these much more frequently than in the arteries. Among 8,356 cases from the London Fever Hospitals thrombosis occurred in 171 (2 per cent.). In this series there were 41 instances (2.7 per cent.) with the following distribution: femoral 23, popliteal 5, iliac 5, veins of the calf 5, internal saphenous 3, common iliac 1, axillary vein 1. In distinction to arterial thrombosis, a great majority occur in the veins of the leg; thus in this series the site was in the veins of the arm in 1, and in the veins of the leg or in the iliac in 40. There is always a preponderance on the left side. In this series thrombosis was on the left side in 28, on the right side in 5, and on both sides in 8 patients. The onset is usually in the third week or later, about half of the cases occurring in the third or fourth week. In about one-

Fig. 12.



Chill at the onset of thrombosis.

third of the cases, thrombosis appears after the temperature is normal. The first symptom is pain which varies a good deal in its severity and mode of onset. In the femoral vein it is usually referred along the course of the femoral vessels but sometimes lower down in the leg. In iliac thrombosis there is usually sudden sharp abdominal pain and, as this may be associated with tenderness and leukocytosis, perforation is suggested. In thrombosis of the lower veins of the leg the pain is usually referred to the vein but in some there may be indefinite pains in the calf. Even in femoral thrombosis, pain may be referred to the calf for two or three days before there are any definite signs.

There is usually some fever with the onset, either an increase in the previous temperature or a reappearance of fever if it has been normal. In only

3 of this series was there absence of fever. In a considerable number a chill occurs, as in 11 of this series (Fig. 12). This may be at the onset or during the height of the process. As a rule there is some œdema, except in rare instances in which the saphenous vein and deep veins of the calf are involved. The swelling is often evident in the femoral region in femoral thrombosis before there is any œdema of the leg. There is frequently some local redness over the affected vessel. In a considerable number the thrombotic mass can be felt as a palpable cord. Although instances of detachment of a portion of the thrombus are rare it is well to bear in mind that the thrombotic mass should be palpated as little as possible. Leukocytosis occurs in the majority, the highest count in this series being about 25,000. Of the cases with thrombosis, 5 resulted fatally but only 2 as a result of the thrombosis—one with axillary thrombosis from pulmonary embolism, and the other with thrombosis in the left iliac vein from embolism of the inferior vena cava and right auricle. While in many instances the process is probably due to a local condition in the wall, associated with the presence of typhoid bacilli, yet in others there may be a second infection. Thus in 7 of this series some other condition was present, such as boils, otitis media, etc.

While not serious as regards the prospects for recovery, thrombosis causes a great deal of annoyance, discomfort, and sometimes considerable suffering. It may greatly lengthen convalescence. Gangrene may occur but is rare. The subsequent history often shows that thrombosis leads to more or less permanent disability, depending largely on the vessel affected and on the extent to which the collateral circulation can be established. In probably every instance of thrombosis of the larger vessels there is some permanent change. The persistent swelling, especially after use, and the formation of varices are both very annoying. The varicosities may be associated with ulceration. There is often marked weakness of the affected limb and sometimes troublesome muscular cramps, especially after overexertion.

Of the causes of thrombosis we know little. That mechanical factors are important is evident from the unequal distribution in the two femoral veins. In some instances the general condition is thought to a factor, as shown by the term "marantic thrombus." It seems probable that a local phlebitis is the cause of many of the cases. This is not necessarily followed by a complete plugging of the vessel, and it may be that phlebitis without much thrombus development is more common than is usually supposed. Wright and Knapp have suggested that the large amount of calcium salts supplied by a milk diet may favor thrombosis. To lessen the risk of this they suggest giving citric acid or causing partial decalcification of the milk by adding citrate of soda (gr. 20 to 40 to the pint).

Blood.—The blood shows important changes. At the onset and for the first two weeks there is little change in the red cells but usually in the third week a diminution in their number appears which goes on as long as there is fever. In long attacks the corpuscles may begin to increase before the temperature is normal. The number of red cells may be temporarily increased by profuse sweating, diarrhœa, or vomiting. A sudden loss may occur with hemorrhage. As a rule the average loss of red cells is about 1,000,000 per cmm. There is generally a drop in the hæmoglobin, which as a rule is reduced more than the red cells proportionally and returns more slowly to normal. The appearance of many of the patients who have passed through

a severe attack gives no accurate idea of the condition of the blood as they look much more anæmic than they really are.

Leukocytes.—The changes in their number are of considerable importance. As a rule throughout the course, the number is diminished and this decrease is to some extent progressive with the severity and duration of the disease. There is a certain degree of individual peculiarity and it is well to know the usual number of leukocytes in every patient. This is especially important if the leukocyte count is to be of any value in the diagnosis of complications. Thus in one patient they may average 5,000, while in the next they may be only 2,500. With the onset of suspicious abdominal symptoms, a count of 6,000 would be much more significant in one patient than in the other. There is naturally a certain normal variation but in uncomplicated cases they rarely reach 10,000 per cmm., and 4,000 to 5,000 may be regarded as about the average. The baths, especially at the lower temperatures (70°), may cause temporary increase in the number. In the differential count the most marked change is an increase in the mononuclear elements and with this the polymorphonuclears and eosinophiles are decreased. With temporary increase in the number of leukocytes as with the baths, the relative proportions remain practically the same. In severe attacks, especially with a protracted course and marked toxæmia, the leukocytes may gradually decrease until they are 1,000 or even lower. This steady drop with severe toxæmia is usually of grave import. The usual low count is an important aid in diagnosis. It assists especially in the recognition of septic conditions, and in a patient admitted with abdominal symptoms suggestive of appendicitis the leukocyte count is most helpful.

The most important conditions under which leukocytosis occurs may be grouped as follows: (*a*) Various septic processes, such as furunculosis, abscess formation, etc., are nearly always accompanied by leukocytosis, which may even follow abrasions of the skin. (*b*) The various inflammatory complications such as pneumonia, phlebitis, cholecystitis, etc. (*c*) *Hemorrhage.* This is frequently followed by leukocytosis, which begins very soon after the bleeding and reaches its maximum as a rule within twenty-four hours. (*d*) *Perforation.* Safe conclusions from the leukocyte count can be drawn only if there have been careful counts beforehand. It is also essential that with the onset of symptoms counts should be made every hour. If they are made at intervals of four hours, a slight leukocytosis lasting for only two or three hours may be completely overlooked. The various changes in the leukocyte count with perforation may be grouped as follows: (1) Preperforative leukocytosis may occur. This is thought to be due to a local peritonitis about the deep ulcers before they actually perforate but is probably very rare, especially as at autopsy the peritoneum over the deeper ulcers may be found markedly inflamed (without peritonitis), while during life these patients did not have any leukocytosis. (2) There may be no increase in the number or even a diminution after perforation. Repeated counts are necessary before one can be certain of this. Such a condition suggests either a very severe infection with marked prostration or that the peritonitis is of a malignant type. As a rule these are extremely grave cases and offer little chance of recovery after operation. (3) There may be a slight leukocytosis lasting for only two or three hours and then a rapid return to normal for that patient or even below the normal. As already stated this will be recognized only if frequent counts are made. (4) Marked leukocytosis may occur, and this

may show a steady increase from hour to hour. Such an increase is not necessarily due to perforation and may be some other acute condition. In others there may be a fairly marked leukocytosis which remains at about the same point. The association of leukocytosis with the degree of infection does not follow any rule, but in general terms it seems true that with a severe, acute abdominal infection, especially with streptococci, the leukocytosis is not likely to be marked. As a rule the differential count shows variations from the usual figures, as the polymorphonuclears may not show the relative increase which usually occurs with leukocytosis.

Late Effects on the Circulatory System.—The view has been gaining ground that typhoid fever may cause more permanent changes in the vascular system than was formerly thought. Thayer[1] has studied this in 169 patients of this series. Examination of the heart showed that the average size was greater than in the same patients on admission to the hospital. In 12 patients, who were discharged with apparently a normal heart, evidence of organic disease was found, 8 of these having mitral insufficiency with hypertrophy. Of 31 patients who had a systolic murmur during the attack, 20 had a murmur which in 5 was evidently of mitral insufficiency and in 1 of mitral stenosis. In the other patients a diagnosis of organic disease could not be positively made. The radial arteries were palpable much more frequently in the individuals who had had typhoid fever than in a control series, the figures being 48 and 17 per cent. This was supported by the observation that in a study of the frequency as to the palpability of the radial arteries, of 943 patients in whom the radials were felt, nearly 20 per cent. gave a history of typhoid fever, while of 231 who had not palpable radials only 10.8 per cent. gave a history of the disease. One patient who had arteritis with possible parietal thrombosis in the left femoral artery showed enlargement of the affected leg and gave a definite history of intermittent claudication. The pulsation in the femoral and dorsalis pedis vessels was equal on the two sides but the posterior tibial pulsation was much weakened on the left side.

It is difficult to speak with certainty of the results of changes in the aorta. These are frequently found at autopsy and undoubtedly exist in many patients who recover. In 62 cases in which the condition of the coronary arteries was carefully noted there were 19 with definite sclerotic changes, in 13 of which the process was apparently recent. In 4 other cases yellow opacities in the intima were noted.

Observations on the systolic blood pressure showed that the average in those who had typhoid fever was uniformly higher than in those who had not had the disease. These all suggest that in certain patients typhoid fever does permanent damage to the vascular system.

The subsequent condition of the veins was noted in 9 patients who had femoral thrombosis during the attack. In all there had been more or less disability and the affected leg was larger than the other. In 6 there had been œdema for varying periods and in the same number there had been pains in the leg, especially at night and after exercise. In all there were marked varicosities, which in 6 extended to the epigastrium. In 2 patients who had double iliac thrombosis, there were extensive varicosities over the abdomen, thighs and legs. After thrombosis of the popliteal vein there was

[1] *American Journal of the Medical Sciences*, 1904, vol. cxxvii, p. 391.

enlargement of the affected leg, and after involvement of the veins of the calf there was enlargement and in one patient œdema with varicosities.

The Nervous System.—The manifestations in the nervous system are the most important and interesting of the disease. The older writers were well inspired when they gave it the name of "nervous fever." There are very few patients who escape without some nervous manifestations and of these headache is the most common. It is a frequent early symptom which may persist throughout the attack or disappear during the second week. It may be referred to one area, often the frontal or occipital region, while in others it is described as a dull, heavy pain felt especially in the vertex, and in some patients it may have a marked neuralgic character, affecting especially the orbital nerves. The headache is often made very much worse by noise or movement. It may continue throughout the course but in the majority, as the general features of the disease become marked, the headache lessens or no complaint is made of it. It is an old observation that epistaxis sometimes greatly relieves the headache.

There are certain symptoms, most common early in the disease, which may be referred to the nervous system. These include indefinite pains in the back and sacral regions, general malaise, with at times roaring in the ears, dizziness and vertigo. Insomnia is sometimes marked early in the attack. As the disease progresses there is usually some dulness and stupor which may be of a very varying character. The patient lies quietly, apparently normal mentally, but when questioned it is evident that there is some delay in cerebration and difficulty in answering anything which involves a test of memory. It is not easy to obtain the history from such patients and after being questioned, they are glad to drop back into a quiet, drowsy state. There are all grades between this and a condition in which the patient is either actively delirious or in coma vigil. There are certain patients in whom instead of stupor there is a condition of marked alertness. They are usually keen mentally and their sensory perceptions may be very acute. This applies especially to hearing and should be kept in mind, as these patients may hear remarks made some distance away from the room. They are often very wakeful and suffer from continuous severe headache.

The patients usually go along in a fairly comfortable condition; they doze and wake without much difficulty; they are easily roused for nourishment and readily fall asleep again. In this group it may be difficult to estimate exactly the mental condition. Thus a patient may be to all appearances clear mentally and yet when the attack is over have no recollection of events which have occurred. Examples are seen in the visits of friends or of a consultant. The patient may recognize a visitor and converse with him but later have no recollection of it. This is of importance in regard to business affairs or the making of a will. There are instances of patients, who mentally were apparently perfectly normal, making a will and after the attack having no memory of it. The majority have little idea of time. Three or four days may seem to them no longer than a couple of hours, or the period spent in a short sleep may seem a week. This is common and should be kept in mind in considering statements made by the patient, as one who has been fed a short time before may say that he has received nothing for twelve hours. Through credence given to such statements, unjust suspicion has been thrown on the nurse.

The degree of stupor varies greatly; it may be slight and perhaps most marked toward evening or through the night. These patients often show restlessness, try to get out of bed and wander about. The gentle restraint of a draw-sheet is often enough to prevent this. The condition may progress farther so that the patient lies in a dull state, taking no notice of his surroundings and oblivious of what is going on about him. This may be of all grades but it is usually possible to arouse them, although no intelligent replies may be obtained to questions. It is difficult to arrive at any clear idea of the mental processes in such states. If the patients can be made to talk it is doubtful if the information obtained is of much value. In rare instances they will give accounts of fantastic dreams and sometimes wake up out of sleep apparently much alarmed At times there may be marked irritability and the patients complain of the nurses and attendants, resenting everything which is done for them. This seems more frequent in patients who were irritable and neurotic before the attack. Great self-control is necessary in those who are handling such patients, as their actions and statements may be very annoying. Children often show marked irritability and they will whine and cry almost constantly when awake and resent all forms of treatment.

A distinction has to be made between stupor and sleep. The patient who is apparently quiet and sleeping may be only in a dull condition and may go for days without any sleep. The extreme grade of this condition is termed coma vigil, a state in which the patient lies quietly, with open but unseeing eyes, sometimes seeming to follow the movements of those about him but really quite oblivious to his surroundings. These patients sometimes make an effort to talk but the result is usually a meaningless jumble of words. While in the majority the tendency is toward stupor yet in a number the delirium is of a more active character. This may be of all grades. The patients may be restless, active and noisy, with periods of special excitement at times. Their various impressions are apparently acute and sometimes of an alarming nature so that they wake out of sleep quite disturbed. Many of these are on the border line between delirium and a psychosis. Individuals react very differently to fever and toxæmia; very neurotic patients may be easily upset and certain persons become "flighty" with even slight fever.

It may be difficult to distinguish between a condition due to the effect of fever on an irritable nervous system and that due to severe toxæmia.

Psychoses.[1]—These occur more frequently with typhoid fever than any other acute disease. It is convenient to follow the classification of Kraepelin, who divides them into (*a*) the initial delirium, (*b*) febrile psychoses, and (*c*) asthenic psychoses.

(*a*) *Psychosis at Onset.*—This is not common but as a rule is severe and patients have been committed to asylums under the idea that they were insane. In other cases they wander away in a dazed state and perhaps are found long distances from home, quite unable to give any account of themselves. Thus one man was brought in by the police, having been found wandering about the streets and not able to give his name or address. This may be termed a confusional state. In others the features are more like

[2]There is no general acceptation as to what should be considered a psychosis in typhoid fever. Some writers regard every instance of delirium as a psychosis, while others hold that febrile delirium does not imply this. The subject has been considered by Farrar. *American Journal of Insanity*, 1902, vol. lix, p. 17.

those of mania. These patients are often violent, attempt to escape from their surroundings and are prevented with difficulty from injuring themselves. In this group are many of the instances of patients who crawl into freight cars, barns, etc., and remain concealed for days. The features are those of an acute intoxication. These early manifestations are likely to occur in individuals who have a psychopathic tendency. The patients belong to two classes, one showing the features of a maniacal state, the other of more or less confusion. The prognosis in the first group is grave, death occurring in a large percentage; changes have been found in the cortical cells.

(*b*) *Febrile Psychosis.*—This is the largest group. The etiological factors are probably two, fever and toxæmia. Different writers ascribe a varying degree of importance to each of these. While it must be recognized that fever may be largely responsible for mental features, yet from a clinical standpoint one is impressed by the importance of toxæmia as seen in patients without high fever but very toxic. On the other hand, some patients show a marked improvement in the mental state with any drop in temperature. The definite psychoses, as Farrar says, show no distinct clinical type but have only the specific etiology. They are very various and difficult to classify but may be divided into (1) conditions associated with hallucinations, which by some writers are described as partial or acute insanity, (2) maniacal delirium, and (3) stupor.

1. In this group come what may be regarded as the most typical examples of psychoses. Among these there are many instances of patients having curious ideas about their bodies. An example of this was seen in a patient who had been at times delirious and rather restless. One day he was found in great distress because he thought he had lost both his arms. He held up his hands to show the stumps and nothing that could be done with his hands would convince him that he still had them. In his condition it was not possible to determine definitely the state of sensation in the hands. Some of these ideas may be very grotesque. One patient imagined that all his abdominal viscera had been removed, which naturally gave him extreme distress, but with convalescence this idea gradually disappeared. Another declared that his "insides were rotten" from having soaked up water in the baths; later he thought his legs had dropped off and that new ones were growing. In some, delirium would not be suspected unless all the circumstances are known, as shown by an intelligent woman who had done a certain amount of nursing. She had a moderate attack and was apparently perfectly clear mentally. She complained of rather severe abdominal pain, which was relieved by stupes, and she had a comfortable night. Next morning she gave a most detailed, circumstantial account of having had an attack of appendicitis and of the operation which had been performed during the night. She gave the name of the surgeon and his assistants, with details of what they had said to her. When an attempt was made to examine the abdomen she begged us to be careful not to disarrange the bandages. She seemed so clear mentally and told the story with so much detail that anyone seeing her for the first time would have accepted it as true. In a few hours she realized that she was mistaken and had imagined the whole story, but for some time whenever she was a little confused, as after waking from sleep, the ideas would return.

The frequent occurrence of these conditions in the colored patients is striking and they furnish a relatively large proportion. In many the delusions

are especially associated with horses and teaming. This may be due to the fact that the colored ward is close to a street on which a good many wagons pass, so that the patients can hear the men calling to the horses. This type of delusion regarding occupation has been seen more in the male than in the female colored patients. In other cases the patients' delusions may be associated with the idea of getting out of the hospital. Thus one patient with a moderately severe attack had been rather excited and restless during the early part of the disease but had done well. On the sixteenth day she was delirious. On the twentieth day she had distinct delusions. She thought her husband was in the ward and that he had ordered her to put on her clothes and go home. This gave her great distress and she cried constantly for her clothes and to be let go. Four days later the temperature became normal, the symptoms cleared and she was discharged well on the thirty-sixth day. In others there may be periods during which the patient is in an exalted mental condition alternating with periods of depression. These seem to be more common towards the end of the attack.

2. Maniacal delirium may occur during the course. Thus one patient who had profuse hemorrhages seemed so weak that one would have thought he could not get out of bed. He had been rather irritable for a day or two but no special change had been noted. He suddenly jumped out of bed and attacked the orderly who was in the room. The patient was able to overpower the orderly and succeeded in putting him on the floor partly under the bed. It was only by the aid of the house officer that the patient was put back to bed. During the struggle he fought furiously and succeeded in biting the physician's hand. He was given morphia hypodermically and after a few hours' sleep woke up in a perfectly quiet condition.

3. The condition of stupor needs no special description. The patients may lie perfectly quiet or in a muttering delirium. From the words which can be understood it may be evident that they have delusions of various kinds. Others may lie quiet and refuse to take any nourishment. This type is usually most marked after the febrile period. These febrile psychoses may terminate with the fever or persist into convalescence. Belonging to the first group are the majority of those which are associated directly with the fever and toxæmia. In the majority the duration is not more than a week. Only a very small number, given by Kraepelin as 3.2 per cent., last for a year.

(*c*) *Asthenic Psychoses.*—It is easily seen how favorable the time of convalescence is for the development of a psychosis. The long duration of fever and toxæmia, the marked emaciation, anæmia which may be present with or without hemorrhages, all favor the development of mental changes. Kraepelin divides this group into three: (1) Isolated delusions or fallacious sense perceptions, (2) conditions of exaltation, and (3) conditions of quiet depression, including states of mental weakness. An example of the first group was seen in the instance in which the delusion that the patient had grown new legs persisted from the febrile period into convalescence. Another was that of a patient who during the fever thought he had been arrested and sent to jail, where he supposed he was. This idea persisted into convalescence and it was with great difficulty that the patient realized that he was in a hospital. The outlook in these cases is favorable; with the improvement in the general condition the psychosis usually disappears.

The second group includes various forms. Thus in one instance there was acute delirium which occurred after hemorrhage with marked exaltation.

Sometimes the patient shows more or less exaltation which continues for some time during convalescence. In others there is a state of depression in which the patient lies perfectly quietly and with this there may be hallucinations. The outlook is always serious, especially when there is difficulty in feeding the patient. The outlook in this group is probably less favorable than in the febrile type, although the large majority of the patients recover. The history before the attack, as regards heredity, etc., is probably an important factor. Mental symptoms may appear some time after the attack. It is difficult to state how long an interval may elapse before an attack of fever can be regarded as without influence on a subsequent psychosis.

As regards the frequency of permanent mental changes after typhoid fever, there is considerable difference of opinion between the clinicians and the alienists. It is natural that the latter should be more impressed by its frequency than the former. Edsall in discussing typhoid insanity has pointed out that the cases are more common than has been generally supposed, but it is difficult to give any positive statistics. It would be interesting if we could determine the incidence of typhoid psychoses under various forms of treatment. With the bath treatment the usual nervous manifestations are greatly diminished in frequency, and it would seem reasonable to suppose that the same is true of the graver disturbances. Another point which has an important bearing on their occurrence is nutrition. It is important to feed these patients as well as possible. It has been noted that if a patient with previous mental disease goes through an attack of typhoid fever, the mental condition may be greatly improved.

There are certain conditions which are difficult to classify. In many patients after recovery there is a state usually termed neurasthenia, which varies all the way from a hypersensitive irritability to depression very close to melancholia. This may quite unfit a man for any work. If he is a laborer he is unable to do heavy work, or if in the higher walks of life there may be loss of memory, irritability and tendency to mental fatigue or confusion after very slight exertion. If the patient persists in endeavoring to work there will soon be marked fatigue and considerable depression. Such patients may be much worried and believe that recovery is not possible. It may be months or even years before complete recovery occurs in such a case. These seem more likely to appear in individuals who had a neurotic tendency before the attack and are undoubtedly favored by too early return to work.

The condition of the memory is interesting. Early in the attack the patient may have almost entire loss of memory so that a history is obtained with difficulty. During the height of the fever there may be almost complete loss of memory even when the patients are apparently not delirious. When convalescence begins the majority of the patients find that the memory is much impaired. This may be for names, dates, and previous occurrences as well as for events which happened during the illness. They may have forgotten things which were known before the attack. Thus the patient may not be able to remember a single line of a poem with which he was perfectly familiar. This is frequently a great worry to patients, but as a rule the restoration is complete although slow. In some patients there may be hysteria or hypochondriasis and with these marked depression. The term mental insufficiency well describes some of these conditions. Occasionally they may pass into more serious mental states.

Hysteria.—Manifestations of this are not uncommon. The patients lie quietly with the eyes shut and refuse to speak, or have typical hysterical attacks associated with crying and noisy demonstrations. When examined, they assume a look of intense suffering associated with patient resignation. Others may complain of attacks of severe pain. Thus one patient complained of intense abdominal pain with which he cried out so loudly that he disturbed the ward. There was pain on palpation and rigidity of the muscles. Soon he became nauseated and vomited. He made so much outcry and was so emotional that suspicion was aroused. The attack subsided rapidly and subsequent manifestations lasted in ratio to the attention he received. In others there may be emotional attacks associated with rapid sobbing respirations. Some of them may be very noisy and scream loudly until exhausted. Others may show frequent rhythmical movements, more especially of the jaw. With these there may be areas of hyperæsthesia, especially over the abdomen. This complicates the diagnosis, especially in patients with abdominal pain, but the recognition of the superficial tenderness is of great help in suggesting hysteria. In other patients there may be marked hysterical dyspnœa or aphonia. In fact, the manifestations may be as various as those usually found with hysteria. A condition closely allied is catalepsy, which occurred in 2 patients of this series. There are usually associated hysterical features and the patient will keep the arm or leg in one position for some time. With this he may lie with the eyes shut, apparently oblivious of his surroundings. The condition is generally of short duration.

Tetany.—This, while a very rare complication, may occur and has been reported as especially prevalent in certain epidemics. Cases have been reported by Janeway. There was no instance in this series, although the writer saw one example recently.

Tremor.—In some degree this is very common and varies from the simplest tremor to conditions which might almost be termed a convulsion. It may occur early in the disease in irritable individuals or alcoholics. During the height of the disease it is usually an indication of the degree of toxæmia. Slight tremor of the tongue is common and of no special significance. There may be tremor of the lips and irregular twitching of the muscles of the face. More serious are the irregular muscular twitchings usually seen most markedly in the arms and trunk. This may be fairly general or involve certain muscles and tendons, the so-called subsultus tendinum, while in others there may be irregular movements of the hands and picking at the bedclothes. Other patients will often pick at the clothing of anyone coming near them, a very common trick being the attempt to take hold of the buttons on one's coat, or the stethoscope, while the patient is being examined. In other cases there may be frequent rapidly repeated movements, especially of the arms. Sometimes there is trismus and a condition almost like tetanus. All these may apparently occur without any organic lesions. If strychnia is being given in large doses the possibility of this being a cause has to be kept in mind but this is readily determined by omitting the drug for a few hours, when the symptoms disappear. There may be quite marked tremor after the attack is over. This usually disappears with increasing strength, but there are instances of its being permanent.

Meningitis.—In some patients at the onset of the attack the meningeal symptoms may be so prominent that meningitis is suspected. The delirium, retraction of the head and rigidity of the neck may suggest meningeal

involvement. Such cases have been termed meningotyphoid. Later in the course the same symptoms may appear. In the recognition of these conditions lumbar puncture has been of the greatest help. The cases in this series have been studied by Cole, who divides them into three groups: (1) Those with symptoms of meningitis in which no lesions were found or no relationship between the bacteria and the symptoms. This has been termed *meningisme*. (2) Those in which the typhoid bacillus was found in the cerebrospinal fluid but without any lesions of a suppurative character. These may be termed serous meningitis. (3) Cases of purulent meningitis.

1. This group should be described as typhoid fever with meningeal symptoms rather than typhoid meningitis. It is difficult to exactly limit the cases belonging to this group. Its recognition is important, as it may lead to a wrong diagnosis at the onset, being regarded as epidemic or tuberculous meningitis, or during the course, when meningitis may be diagnosed as a complication. It is important to remember that all the clinical features of meningitis may be present. Kernig's sign may be well marked apart from meningitis, as in 8 of the last 685 cases of the series. It is important to keep this in mind, as certain writers make the statement that Kernig's sign never occurs in typhoid fever apart from meningitis. In this series the diagnosis of this group was made either by the negative findings of lumbar puncture or by autopsy. It may be noted that well-marked ankle clonus was present in two.

2. *Serous Meningitis.*—In this there is a mild grade of inflammation associated with changes in the meninges, which are microscopic and consist of œdema and round cell infiltration about the bloodvessels. The exudate is serous and apparently usually contains typhoid bacilli. Cole has found 8 cases in the literature and reported 5 from this series. There is usually headache, mental dulness and either unconsciousness or delirium. Convulsions occurred in 4 of the reported cases, while stiffness of the neck and retraction of the head were frequent but not constant. In 2 cases facial paralysis occurred. Kernig's sign was present in 2 cases and absent in 2. The reflexes showed considerable variation. In none of the cases was there a leukocytosis. Death occurred in all the patients of this series but one, but this was not necessarily due to the meningeal condition. The most important point in the recognition is the result of lumbar puncture; in all the reported cases the fluid was clear and only a few leukocytes were found; the amount varied from 20 to 60 cc. Typhoid bacilli were grown from the spinal fluid in all. The pressure did not seem to be greatly increased, but the removal of the fluid seemed to improve the condition. Cole suggests that in the study of the spinal fluid from such cases the following points should be noted: (*a*) Large amounts of the fluid, 4 to 6 cc., should be used for cultures, (*b*) the pressure of the fluid in the spinal canal should be estimated, and (*c*) the character of the cells in the exudate should be carefully studied. The condition may be considered as analogous to that found in the other serous cavities and it may be that future observation will show that this type of meningitis is more frequent than has been supposed.

3. *Purulent Meningitis.*—In this group there is a definite purulent meningitis associated with the typhoid bacillus. Cole has collected 13 cases in the literature which he considers authentic, and there was 1 case from this series. The symptoms show no special difference from those of the serous type. The onset may be early or late but death as a rule follows within a

few days. Delirium, muscular rigidity and incontinence of urine were marked features, but in only 1 case were convulsions noted and in only 1 did paralysis develop. Priapism may be present. Kernig's sign was absent in the case of this series and also in 2 out of the 3 other cases of purulent meningitis and in 3 out of 5 cases of serous meningitis. The spinal fluid contained enormous numbers of typhoid bacilli and many polymorphonuclear leukocytes. Other organisms may set up purulent meningitis; thus, infection may come from old ear disease or be one of the manifestations of septicæmia. Tuberculous meningitis has been observed, as in one patient belonging to the serous type in whom typhoid bacilli were obtained from the spinal fluid during life, and at autopsy fresh tuberculous meningitis was found. It is possible that the meningococcus might cause meningitis during an attack of typhoid fever. It may be noted that meningeal hemorrhage is not common; small circumscribed hemorrhages may at times cause focal lesions, but extensive hemorrhage is rare, although it has occurred in the hemorrhagic type.

Cerebral Lesions.—These are not common. Hemorrhage, thrombosis, embolism, meningo-encephalitis or abscess, may all occur, sometimes in convalescence, and following them there may be areas of softening. It is difficult in many of the cases reported without autopsy to decide with certainty the character of the lesion. Aphasia has occurred in a certain number, at times associated with right-sided hemiplegia. In the literature there are a number of cases, some of which may have been due to minute emboli, but in others it probably occurred without an organic lesion. Bulbar paralysis has been noted and there are a few cases of abscess. Hemiplegia occurs during the course or in convalescence. The condition shows no special peculiarity. Paraplegia is not common. Some of the descriptions in the literature rather suggest that the weakness of the legs which sometimes follows an attack may be due to it. Gowers mentions that some patients never seem to be able to walk as well after an attack of typhoid fever. Monoplegias have been reported, but there is always a suspicion that they are instances of neuritis. There are cases reported as having general choreic movements but there is always the possibility that they were true chorea. Instances of paralysis agitans coming on after typhoid fever are also described.

Spinal Lesions.—These like the cerebral are comparatively rare. Myelitis may occur and in a case reported by Curschmann was definitely associated with the typhoid bacillus, which was obtained in sections and cultures. Poliomyelitis has also been observed in some instances secondary to typhoid fever.

Reflexes.—There are many positive statements regarding the reflexes but it does not seem possible to give any constant rule. They may be exaggerated or entirely absent and this variability is seen in ordinary attacks or in those with lesions such as meningitis. The state of the reflexes may vary from day to day. Kernig's sign and ankle clonus may be obtained in patients who apparently have no organic nervous lesions.

Convulsions.—These are extremely rare, there having been only 7 instances in this series. They may occur under various conditions, (*a*) at the onset, as is especially likely in children. (*b*) During the course and probably as a result of the toxæmia. These are not common and the toxæmia is only suggested as a possible explanation. In one patient who was very

toxic there were repeated convulsions, but he made a good recovery and no other cause could be found. (*c*) A group due to cerebral complications, such as embolism, thrombosis, hemorrhage, etc., which are always serious. (*d*) In convalescence. These are puzzling and it may not be possible to give any explanation, although in some instances they are due to hysteria. (*e*) With other conditions, such as epilepsy or uræmia. An epileptic who has typhoid fever may have his usual convulsions, although generally they occur rather less frequently during the fever. Some writers consider that epileptic seizures are likely to be rather common during the attack. The instances of convulsions due to epilepsy are not included in the 7 cases noted above. Convulsions are always serious, not from any danger in the convulsion itself but because they may be due to a serious cerebral complication. Of the 7 cases in this series 3 died. It has been suggested that in some they are due to œdema of the brain or to local vasomotor changes. Renal disease was the cause in one patient admitted with uræmia, who died in a few hours after several convulsions. The autopsy showed a small sclerotic kidney and also the lesions of typhoid fever.

Neuritis.—This is not common and occurred in 11 cases of this series, or .7 per cent. This does not include the instances of tender toes. Neuritis may occur during the latter part of the disease or in convalescence. It may be either multiple or local.

Multiple Neuritis.—As a rule this comes on during convalescence. The four extremities or the legs may be involved. It may be difficult to diagnose from poliomyelitis and it is probable that some of the cases in the literature put down as spinal disease are really neuritis. Some instances of multiple neuritis are regarded as due to the alcohol given during the attack.

Local Neuritis.—This may come on during the attack but more commonly with defervescence and convalescence. The pain is often very severe and there may be great tenderness on pressure over the nerve, with marked wrist or foot drop in some cases. In others there may be marked swelling of the affected limb and considerable circulatory disturbance. The conditions which may result are very various; thus there may be quite marked contractures, atrophy, curious trophic disturbances, chronic contractions of the muscles and sensory disturbances. There are some conditions which suggest a slight grade of neuritis. One of these is weakness in the legs which is found when the patient begins to go about and as a result he has a curious, uncertain gait. The majority of these suggest muscle rather than nerve changes. In others there may be a certain amount of pain which is referred to the course of a nerve, especially the sciatic, but as a rule this is not severe and clears up in a short time. Meralgia paræsthetica has been reported as a sequel. In other cases there is considerable tenderness which is rather ill-defined but increased by pressure on the muscles. This also suggests myositis rather than neuritis. In all such cases the possibility of a slight thrombosis must be kept in mind.

Tender Toes.—This is regarded as being a local neuritis. It may come on during the height of the attack or in convalescence but is rarely seen early in the disease. The toes, especially their plantar surface and occasionally the adjoining part of the foot, become extremely painful. The patients usually complain first of the pain caused by the pressure of the bedclothes, but it often increases so that they cannot bear any weight or the gentlest touch. It is not uncommon to find emotional patients crying with the pain

but it rarely lasts more than a few days in a severe form. Examination is practically negative and there is no redness or swelling. It is generally supposed that the condition is more likely to occur in patients who have had the baths but it may be seen in patients who have had alcohol sponges only, and has been noted after an attack so mild that no hydrotherapy was necessary. Under the bath treatment the thoroughness with which the patients are rubbed has a certain influence on the occurrence of tender toes. The more thoroughly and carefully the feet and toes are rubbed while the patients are in the tub the less frequently tender toes occur.

Special Senses.—In general terms it may be said that involvement of the special senses is comparatively rare.

The Eye.—The ocular complications have been especially studied by Bull and de Schweinitz. Catarrhal conjunctivitis occurs during the febrile period, especially in severe attacks, and is probably associated with the decrease in secretion. Keratitis is rare but has been seen in severe attacks. Iritis, choroiditis and inflammation of the vitrous have all been noted, while cataract has been observed in a few cases. Retinal hemorrhages are said by Bull to occur fairly often, and may be part of the manifestation of the hemorrhagic type. Embolism is extremely rare. Double optic neuritis has been noted, which may occur with meningitis or as a local process. Hemorrhage into the optic nerve is rare. Optic nerve atrophy has been noted. Paralysis of both the intra- and extra-ocular muscles may occur, and there was one instance in this series of paralysis of the extra-ocular muscles which came on early in the attack. Slight local meningitis seems the most reasonable explanation. Little attention has been paid to changes in the pupil during typhoid fever. Ptosis has been observed. Amblyopia has been noted rarely. Thrombosis of the orbital veins has occurred but is rare.

The Ear.—Excluding conjunctivitis, affections of the ear are much more frequent than of the eye. Early in the disease there may be subjective disturbances, the patient complaining of roaring in the ears. Deafness without any discoverable lesion occurs comparatively frequently and is often common in certain years and rare in others. It may occur at the onset or usually more markedly during the course, and may appear suddenly or develop gradually during two or three days. In some patients it may be difficult to decide whether deafness or stupor is the more important condition, and in those who are deaf the lack of attention to questions has been ascribed to stupor. The explanation of deafness is difficult to give, but the subsequent course shows it is usually not a neuritis. As a rule recovery is complete but in some the disturbance may last during convalescence and occasionally it may be months before hearing is restored. Such cases and those with a permanent loss of hearing suggest a neuritis, although a local meningitis may be the cause. As a rule the outlook is good and the patient is left with the hearing unimpaired. Otitis media is quite common and its frequency varies greatly from year to year. Hengst among 1,228 cases found it in 29 (2.3 per cent.) and in this series it occurred in 21 patients (1.4 per cent.). The ears should be frequently examined, as dull patients may make no complaint of pain and the condition is recognized only with the appearance of the discharge. In some it is merely the lighting up of an old process but in others it is probably due to extension from the throat. It is usually not serious, although it may extend to the mastoid. In this series there were several patients with redness and swelling over the mastoid without any otitis,

but in no case was operation necessary. The possibility of extension to the meninges has to be kept in mind. The organism present is usually one of the pyogenic cocci. In no case of this series was the typhoid bacillus found in the discharge but there are a few instances in the literature. In some patients the otitis may appear during convalescence and be the cause of an elevation of temperature.

The Nose.—Special disturbances here are rare. Some patients complain persistently of disturbed nasal sensations. They smell a foul odor, although this is not perceptible to others, either about the patient or in the discharge from the nose.

The Renal System.—In this are changes due to the febrile state, which show no special difference from those due to any fever, and also those peculiar to the typhoid infection. The urine is usually diminished in amount, with abundant sediment and increased pigments. The specific gravity as a rule is increased and the reaction is strongly acid during the height of the attack, later often becoming neutral or alkaline. The amount of urea and uric acid is increased and may be double the normal, while the chlorides are decreased. This description has to be altered if large amounts of water are given, for if the amount of urine be thus increased to three liters or more *per diem*, the color is pale, the specific gravity much lower, 1,015, 1,010, or even less, and the reaction is very feebly acid, neutral or alkaline. If large amounts of urine be passed, such as six or more liters, the specific gravity may fall even lower, to 1,001 to 1,005, and the color be very pale. The investigations of Sollman and Hofmann on such cases showed that the eliminating capacity of the kidneys was not injured. There was no accumulation of fluid in the body and the total chloride secretion was increased. Diuretics did not increase the amount of urine.

Polyuria.—It should be the endeavor to produce this in every patient. The amount of urine passed is usually an index of the quantity of water given. In patients who are not being given this "washing out treatment" a sudden polyuria may be observed, usually toward the end of the attack, although it may appear at the height of the fever. This is analagous to the polyuria seen in other acute diseases, such as pneumonia.

The statistics of albuminuria vary greatly. Thus Curschmann gives 15 to 20 per cent., but in this series albumin was present at some period in 999 cases (66 per cent.). Casts were found in 568 cases (37.8 per cent.). In a large number albumin was found only during the first few days after admission. Thus, among the last 685 cases, albumin was found only on the first four days after admission and was not present afterward in 175. In many of these it was found only during the first day in the hospital. This is not peculiar to typhoid fever, being seen in other febrile conditions. Albumin in the urine is ordinarily due to two causes, (*a*) the febrile state, and (*b*) changes in the kidney. It is difficult to decide the number of each but in the great majority it is due to the former. In 150 others of the last 685 cases the albuminuria persisted through a considerable part of the attack. The point made by Curschmann that febrile albuminuria renders the prognosis distinctly graver does not seem to be supported by the large number in this series.

The amount of albumin varies but in many is a mere trace, especially when present for a short time only. Tube casts may be found but are usually scanty. The duration of albuminuria is rarely more than ten days, although

in some patients, what was regarded as febrile albuminuria persisted throughout the greater part of the attack. Severe anæmia may be a cause of albuminuria.

Among the special conditions is the onset with acute renal features, the *nephrotyphus* of the Germans or *forme renale* of the French. There was only one instance in this series. It is regarded as a serious condition.

Pigments.—There may be marked increase of the pigments. Urobilin and indican may be found in large amounts but it is doubtful if either has any special significance. Patients with large amounts of indican in the urine may have mild attacks with a complete absence of any special features. The increase of indican cannot be considered of importance in the recognition of the onset of peritonitis, nor does it necessarily mean any special intestinal condition.

The Diazo Reaction of Ehrlich.[1]—The reaction was given in 61 per cent. of this series. In case of doubt the tube should be let stand for twenty-four hours, when a greenish precipitate is deposited if the reaction is given. The frequency of its occurrence is much diminished if the patients are passing large amounts of urine, or if present the reaction may be given very feebly. In such it may be obtained by evaporating the urine down to a quarter of its bulk. It may be present in the first three or four days or appear as late as the fourth week and may return with a relapse. Its value for diagnosis is distinctly lessened, as it occurs in other diseases, such as malarial fever, acute tuberculosis, pneumonia and some of the acute exanthemata. The reaction depends on incompletely oxidized products of nitrogenous metabolism which belong to the aromatic compounds. Acetone is often found in the urine (12 per cent. in some series) and β-oxybutyric acid occasionally. The excretion of phosphates is diminished during the attack and increases with defervescence. The methylene blue reaction described by Rosso does not appear to be of any special value.

Bacilluria.—This term in typhoid fever is usually applied to the presence of typhoid bacilli in the urine, although strictly speaking it includes any organism. The bacteriological study of the urine has increased our knowledge of the disease and thrown light on its transmission. It is only in recent years that we have realized how often typhoid bacilli are present in the urine and for how long a period they may persist without causing any symptoms. The incidence of bacilluria will vary with the epidemic but especially with the care with which the urine is examined. In many patients the condition is transient, only a few bacilli may be present, and without frequent careful examinations these will be missed. It seems reasonable to state that bacilli are present in the urine in from 20 to 25 per cent. of all cases.

Bacilluria does not seem to be associated with the severity of the attack and in this probably lies a great danger in the spreading of infection. The number of bacilli varies; there may be only a few or they may be so numerous that the urine has a distinctly turbid appearance. This is sometimes so characteristic that the diagnosis can be made at a glance by holding a test-tube full of urine up against the light, when a curious shimmer is seen. The number of bacilli in the urine has been estimated as sometimes amounting to several hundred thousand millions *per diem*. The explanation of their occurrence is difficult. That they are derived from the bacilli in the blood,

[1] The technique of this is described in works on laboratory methods.

being passed out as it were, does not seem an adequate explanation as the periods of greatest frequency in the blood and urine do not correspond. Nor does it seem probable that local conditions in the kidney can be a frequent cause. Direct passage through the bowel and bladder wall is a possibility but probably does not occur frequently. In rare cases their presence may be due to local processes in the bladder itself. The suggestion made by Horton-Smith that they are derived from stray bacilli which reach the bladder and there find conditions favorable for multiplication, seems the most likely explanation. The curative results of local treatment support this.

Bacilluria does not necessarily cause any symptoms unless cystitis occurs. The urine may show gross changes but microscopic examination is necessary if the bacilli be in small numbers. The presence of actively motile bacilli in freshly voided urine is very suggestive. Cultures are necessary to render the diagnosis certain, and care must be taken to differentiate the organism from the colon bacillus. Bacilli rarely appear in the urine before the third week and may be found for the first time in convalescence. With bacilluria there may be albuminuria, pyuria or cystitis, but they are not necessarily associated. In addition to the typhoid organism the colon bacillus and various cocci may be found. Bacilluria may persist for many years.

Pyuria.—This occurs in a number of cases but the exact percentage varies with what is considered pyuria. In many patients a few pus cells may be found but such can hardly be included under this term and in females only the examination of catheterized specimens can be considered. Pyuria does not usually give rise to any symptoms, and it is not necessarily associated with pyelitis or cystitis. It is frequently associated with the presence of organisms. The possibility of an associated gonorrhœa being the cause has to be kept in mind. The gonococcus and typhoid bacillus may be together in the bladder.

Hæmaturia.—As a rule this is associated with conditions in the kidney, although the frequency of changes in the mucous membrane of the bladder suggests that in some cases these may be the source of hemorrhage, as is undoubtedly true of some cases of cystitis. The amount of blood does not bear any definite relation to the severity of the renal condition. Hæmaturia is of importance only as indicating other conditions. Although necessarily of grave omen, there are many instances of recovery. Hæmoglobinuria is a rare and serious condition, present in two cases of this series. In a case reported by Musser and Kelly, there was hæmoglobinæmia with the hæmoglobinuria.

Acute Nephritis.—This may occur at the onset—nephrotyphoid—and may quite conceal the true nature of the condition. It is often difficult to separate febrile albuminuria from slight nephritis and one may pass into the other. On this account it is difficult to state the frequency of acute nephritis with any certainty. In this autopsy series it was present in 8 out of 105 cases, in 2 of which it was hemorrhagic. Curschmann puts the incidence at scarcely 1 per cent. In the clinical series 10 patients were regarded as having acute nephritis. There are rarely any symptoms suggestive of uræmia, and œdema is uncommon. As a rule if the patient recovers, the renal condition clears up completely and the acute nephritis rarely becomes chronic. There has been no such case recognized in this series. Chronic nephritis was found at autopsy in 6, having been present before the attack of fever. Nephritis during convalescence is rare.

Pyelitis.—This may occur during the height of the disease or in convalescence, and may be difficult to distinguish from cystitis. There may be blood and pus in the urine at first, the pus continuing. Severe pyelonephritis may occur but perinephritic abscess is rare. The diagnosis of pyelitis may offer considerable difficulty. In some patients during convalescence there was a sudden increase in temperature with pain referred to one kidney. With this there was tenderness on palpation in the region of the kidney, a sudden increase in the amount of pus in the urine, accompanied in some cases with a little blood. Several of the patients showed a marked leukocytosis. Such a picture suggests acute pyelitis. The condition cleared up entirely in all after a few days. A definite pyelitis was found only once at autopsy and typhoid bacilli in pure culture were obtained. In rare instances there may be a post-typhoid pyelitis with ulceration, erosion and the formation of a diphtheroid membrane, which may be associated with a similar condition of the bladder.

There are rare renal conditions such as lymphomatous nephritis, infarcts, abscesses, etc., which are of no special clinical importance. Multiple abscesses were found at autopsy in 7 cases.

Cystitis.—Its frequency is difficult to state. The diagnosis was made in 32 cases of the series (2.1 per cent.). In patients who have bacilluria it is difficult to draw the line between pyuria, slight catarrh of the bladder, and a true cystitis. Cystitis does not necessarily result from the presence of typhoid bacilli in the bladder. Pyuria may occur with the typhoid bacillus but also with the colon bacillus or staphylococci. The cystitis offers no special features. Some patients have practically no symptoms, or there may be some pain with frequent and painful micturition. Cystitis may be the cause of persistent fever, as in one patient who had an irregular temperature of about 100° for over three months. The organism was the colon bacillus. As a rule cystitis due to the typhoid bacillus improves much more rapidly under treatment than when due to the colon bacillus. Acute cystitis was found at autopsy in 4 cases, not including the cases of hemorrhage into the mucous membrane of the bladder, which are comparatively frequent. In chronic cystitis the bladder walls are likely to be thickened and the mucous membrane may show ulceration. This was found in the case reported by Young, in which the infection has existed for seven years. Infection with the gonococcus in addition to the typhoid bacillus may take place. In a case reported by Brown there was infection of the bladder from without by *B. typhosus* which had probably been introduced by a catheter.

Prostate.—Abscess of the prostate was found once at autopsy. The organism present was *B. proteus.*

Urethritis.—This has been noted in rare instances apart from a gonococcus infection. No direct proof of its being caused by the typhoid bacillus has been found.

Retention of Urine.—This is often troublesome and is quite common at the onset, when it may be partly due to the difficulty in urination which many patients have for the first day or two after they are kept in bed. Later in the disease it may be associated with stupor, and in such patients the utmost care should be taken to prevent retention, for if distension occurs the patient is rarely able to void. If retention has occurred there may be no complaint from the patient, but on examination of the abdomen there is a well-marked swelling in the hypogastrium, which may extend up to the

navel. The passage of urine does not exclude retention, as there may be constant dribbling from an overdistended bladder. In some patients there may be severe abdominal pain with distension of the bladder.

Incontinence of Urine.—This is most frequent in patients who are dull and stupid, and may be associated with distension. Every care should be taken to prevent incontinence, or at any rate to prevent the urine soiling the bedclothes; the patients should be waited on frequently, but if this is not effectual some form of urinal or bag should be used.

The Reproductive System.—Gangrene of the genitalia is rare in males, although there are cases in the literature in which the penis and scrotum were involved. In the female it is much more common and Keen reported 17 cases. The process may involve the external genitals or the vagina and cervix. It may extend to the perineum or cause fæcal fistulæ. Suppuration of the glands of Bartholin has been noted, associated with the *B. typhosus* in pure culture.

Ovary.—Abscess of the ovary has occurred and the typhoid bacillus been found in the pus. Abscess in the tube has also been observed, as in a case reported by Scudder, with the typhoid bacillus in pure culture. Hemorrhage into the ovary has been found at autopsy.

Menstruation.—As a rule this ceases during the course of the disease, although at the onset it is not uncommon for menstruation to occur, often with a short interval since the preceding period. During the course of the disease it was present in 11 among the 438 female patients but not with the profuse flow which some writers consider common when menstruation does occur. In the hemorrhagic type, bleeding may occur from the uterus. Menstruation may be a cause of abdominal pain. In patients in whom there is a possibility of pregnancy, hemorrhage due to abortion should not be mistaken for menstruation. It may be some months after convalescence before menstruation re-appears.

Pregnancy.—Among the 438 female patients in this series there were only 6 who were pregnant (1.4 per cent.). Abortion or premature labor occurs in the majority. Thus of 169 cases with full data collected by Sacquin the pregnancy was terminated in 103. Of these, 124 were less than seven months pregnant, of whom 72 miscarried, and 45 were over this period, with premature labor in 31. Lynch concluded that typhoid fever was more often seen in the first half of pregnancy, and that pregnancy was most likely to be interrupted in the third month and in the second week of the fever. Miscarriage occurred in 5 of the 6 patients, the sixth being delivered subsequently of a living child. The occurrence of miscarriage or premature labor adds somewhat to the danger of the disease but not greatly.

The typhoid bacillus may pass from the mother to the child in utero, usually in cases with hemorrhagic lesions in the placenta. The child apparently always dies of the typhoid septicæmia but does not necessarily show intestinal lesions. The agglutination reaction is not always given by the fœtal blood, and if present it may come from the mother's blood or may have been due to changes arising in the blood of the fœtus.

Puerperal infection with the *B. typhosus* may occur. There have been 3 instances in the obstetrical department of the Johns Hopkins Hospital. In one there was a localized lesion in the chorion from which the bacilli were obtained in pure culture.

The Glandular System.—Mastitis.—This is rare and occurred in 4 of this series, 3 being females. In about half the cases in the literature both breasts were involved. Suppuration occurred in about half the cases and in a few instances the typhoid bacillus has been obtained from the abscess or by puncture of the inflamed gland. Mastitis may appear during the attack, usually after the third week or in convalescence. In one patient both breasts were involved during the attack and one for the second time in a relapse. There is usually pain, swelling and tenderness of the breast with elevation of temperature. Leukocytosis is common. The condition does not appear to have any unfavorable influence on the course of the disease. Slight induration of the breast occurs frequently; the patient may complain of pain or the condition may be discovered accidentally. It is of no importance and rarely lasts long. Pain may be present without any induration. In one patient calcification of the breast occurred after an abscess which followed the injection of calcium chloride solution.

No authentic instance of the occurrence of typhoid bacilli in the milk has been found. The agglutination reaction may be given by the milk and was given by the colostrum of one prengant patient on the seventeenth day, while the blood serum gave it on the twentieth day, when typhoid bacilli were obtained by blood culture. The agglutination reaction may be given by the blood of the nursing child, apparently having been conveyed by the milk.

Orchitis.—This is not frequent and was present in only 4 cases of this series (.27 per cent.). As a rule it appears late in the disease or in convalescence. It may come on with a chill, and if the temperature has fallen there is usually marked elevation. In one patient it occurred at the beginning of a relapse. As a rule the testicle is affected first, the epididymis later; the swelling may be marked and the pain is usually severe. In the majority the condition is unilateral. In a certain number suppuration has occurred (in 29 out of 69 cases collected by Blumenfeld), and in some of these typhoid bacilli were obtained. The infection in such cases may be through the blood, but the possibility of its being by continuity has to be remembered. The duration is usually from twelve to eighteen days, and following the orchitis there may be induration or atrophy of the testicle.

Thyroiditis.—This is not an uncommon condition in some localities and is said to be relatively frequent in Switzerland. It is apparently more common in patients who have enlargement of the gland. It did not occur in this series. The symptoms are pain, tenderness and some enlargement of a part or whole of the gland. Dysphagia may occur, especially if the left lobe is involved. The process may clear up entirely or terminate in suppuration and the organism may be the typhoid bacillus or one of the pyogenic cocci. Thyroiditis is most likely to appear in the latter part of the attack or during convalescence. As a rule it is not dangerous, although in few cases there have been serious symptoms from pressure.

Lymphatic Glands.—General enlargement of these may occur but has no special significance.

The Osseous System.—Lesions of the bones are more common after than during the attack. In all the lesions the organism most frequently found is the typhoid bacillus and it is sometimes found in pure culture in the fluid obtained by aspiration of the swelling of periostitis. In a few the pyogenic cocci are present, while occasionally the cultures are sterile. The bacteriological findings in the bone lesions are thus contrary to those in the glandular

complications, where the pyogenic cocci are more frequently found than the typhoid bacillus. We are indebted to Keen for an excellent account of this subject.

Periostitis.—During the course of the disease this is the most common osseous lesion, although it may appear in convalescence or months after the attack. Its frequency varies greatly; thus among 8,356 cases in the London Fever Hospital there were 110 (1.3 per cent.) but only 8 instances in this series (.5 per cent.). It occurs most frequently in the ribs, clavicle, or bones of the extremities. The symptoms are pain, tenderness and swelling, with redness over the affected area. There is rarely any constitutional change. The process may subside and recur later, there may be thickening which persists for some time, or abscess formation may follow. Periostitis is frequently associated with changes in the bone.

Bone Lesions.—The most common lesion is necrosis, then caries, osteitis, and osteomyelitis. It is rare for them to appear during the course; they are more frequent afterward. The only instance in this series during the attack was in a boy aged ten years who had fluctuating masses on the frontal bone and on one rib. The former contained greenish pus, cultures from which were negative; the latter subsided without interference. They appeared very early in the attack. The time between the attack and the onset of bone lesions may be many years, intervals of six and seven being reported. Practically any of the bones may be affected but the majority of cases occur in the leg. There is rarely any fever or constitutional disturbance except in very acute cases, and in the majority the old term of "cold abscess" applies. Pain, tenderness, swelling and sometimes redness are found locally. As in periostitis the course is variable; the process may subside or there may be a recurrence but more commonly there is abscess formation, and if pus is present the condition is likely to become very chronic. If a sinus form or a partial operation be done, suppuration may continue indefinitely and typhoid bacilli persist for years. In some cases there may be a sequestrum present. In rare cases the process extends to the adjoining soft parts or to a joint. This tendency to chronicity and recurrence suggests the necessity of thorough treatment; no half measures are effectual. The outlook is usually good, although there may be danger in the cases of mixed infection.

Typhoid Spine.—This term is used to describe a group of cases in which, usually toward the end of an attack or during convalescence, certain symptoms appear which are referred to the spine. Attention was first directed to it by Gibney in 1889. It usually follows a mild attack and the majority of those affected are males. In few instances the symptoms apparently follow trauma. The onset is rarely longer than three months after the attack. Marked neurotic features are common; pain is the most prominent symptom, is usually in the lower dorsal or lumbar region and may radiate round the body or down the legs. It is variable and may be very severe on movement. There may be difficulty in walking, and bending of the spine be impossible. Swelling of the soft parts, kyphosis and scoliosis have been noted. Rigidity and fixation of the spine, sometimes associated with tenderness, may be found. The reflexes may be altered and symptoms referable to the nerve roots are common, such as severe pain, muscle spasm and cramps, wasting, disturbances of sensation, etc. Fever has been present when the condition occurred in convalescence. The duration varies from weeks to many months and relapse has occurred.

There is much difference of opinion as to the nature of this condition, whether functional or due to organic changes. The neurotic features shown by many of these patients, the fact that suppuration does not occur—especially when we remember how common this is in typhoid bone lesions generally—speak for a functional condition. On the other hand, the deformity, rigidity and signs of pressure on the nerve roots speak definitely for organic changes. The most convincing evidence of organic change is given by the radiograms. In 2 patients (one with a typhoid, the other with a paracolon infection) definite deposits of new bone were shown in the plates. These are reported elsewhere.[1] The proof of bony changes in certain cases suggests that organic conditions of some sort are probably present in many. In some patients the hysterical features are so marked and the evidences of any organic changes so slight that a functional disturbance is suggested. Others complain of pain in the back for months after the attack without having the features of typhoid spine. These, with the instances of persistent weakness of the legs for a long time after an attack, may be examples of slight grades of spondylitis.

It is perhaps best to classify the cases under three heads: (1) those in whom the hysterical features predominate and in whom no organic changes can be found. There is no disturbance of temperature or pulse; the patient may declare that he cannot move his legs, which he does a few minutes later when his attention is directed elsewhere; there may be disturbacnes of sensation. Certain other patients who complain of pain in the back which may persist for months should perhaps be put in this class; the symptoms are not severe and they are usually able to get about without difficulty; some of these suggest mild varieties of typhoid spine. Others have persistent weakness of the legs for a long period and some may belong to this group. While the general neurotic features are the most prominent it is impossible to exclude slight changes in the spine. (2) Periostitis or perispondylitis. The occurrence of fever, pain, rigidity and evidences of nerve root involvement, all suggest a local process. Gibney regarded this as a perispondylitis "meaning an acute inflammation of the periosteum and the fibrous structures which hold the spinal column together." It can readily be seen that even extensive inflammatory conditions may not give any positive local sign of disease. (3) A group with definite changes. It may not be proper to separate these from the former group, as they probably always follow the changes mentioned there. Lord in reviewing the reported cases found mention of deformity in 8 out of 26; these with the occurrence of rigidity suggest bony changes. This has been proved by the *x*-rays plates in 2 patients, the plates showing distinct deposit of new bone in the lower dorsal and lumbar region.

The diagnosis of typhoid spine rarely offers any great difficulty, but the decision as to the exact condition present may not be easy. A previous spondylitis should be excluded. The radiograph should be of help in recognizing the cases with organic bony changes, and in every case of typhoid spine plates should be taken. Tuberculosis of the spine is not likely to give much difficulty. The local pain may be so severe opposite one part of the spine that abscess formation may be suspected. The outlook is good, recovery being the rule. There may, however, be pain and tenderness for

[1] *American Journal of the Medical Sciences*, 1906, vol. cxxxii, p. 878.

months or, in some, years after. Some disability and slight rigidity may persist and relapse may follow strain or injury.

Arthritis.—This is a rare complication and was present in only 8 cases of this series, 4 being monarticular and 4 polyarticular. Arthritis usually arises spontaneously, but in rare cases it may be due to the extension of a bone lesion. The symptoms require no special mention; there is pain, swelling and redness. Arthritis may persist throughout the attack, as in one patient in whom the joints of the right arm were involved on the fifth day. This continued through a long attack, and on discharge on the eighty-eighth day there was still some thickening about the wrist joint. Suppuration and permanent ankylosis are rare. The tendency to dislocation, especially in the hip joint, must be remembered. Keen found that spontaneous dislocation had occurred in half the reported cases, the majority being in young persons. It usually occurs with serous distension of the joint in convalescence. In rare cases the exudate is purulent and a sinus may form. The frequency of dislocation in the hip joint suggests care in watching for the onset of arthritis, and if it appears every effort should be made to prevent dislocation. Except for this the outlook in arthritis is good. If it be part of a septic infection the condition is more serious, but such are rare.

The Muscles.—Degeneration is of more interest pathologically than clinically, for symptoms are rarely observed. Hemorrhage may occur into the substance of the muscle, and should this become infected, abscess formation follows. Rupture is rare and no instance occurred in this series. In the majority it is late in the disease, generally in males, and often thought to be due to movements in delirium. The symptoms are sudden pain and tenderness. There is usually a hæmatoma, and suppuration often follows. The typhoid bacillus has been found in the pus. The complication is a serious one because it usually occurs in severe attacks. In some instances suppuration in the abdominal muscles has extended to the peritoneal cavity, so that it is well to open freely as soon as suppuration occurs in this situation. In some patients there is a condition seen during convalescence which suggests a myositis. There is tenderness on handling or pressing the muscles, which may continue for some weeks but usually gradually disappears. Phlebitis and neuritis must always be excluded.

Abscesses.—No part of the body where abscess may occur is exempt. The typhoid bacillus is the causal organism in a varying number of cases depending on the site of the abscess. In other cases the typhoid bacillus and other organisms—usually the pyogenic cocci or colon bacillus—are associated, or these organisms occur alone. They may be classified as follows:

1. Abscesses in the skin, subcutaneous tissues, muscles, bones and connective tissues. These are common, especially if boils are included. They usually appear late in the disease or during convalescence. If they appear as sequelæ the suspicion of a periostitis being the cause should be considered. Abscesses may be situated anywhere, perhaps most frequently about the buttocks. They are not uncommon in the perirectal region and may be due to perforation in the lower part of the rectum. In the abdominal muscles they may be secondary to a hæmatoma. In some regions, as about the neck, they may arise by extension from one of the glands or from the larynx. They may even extend to the mediastinum. Alveolar abscess is not uncommon, especially in connection with carious teeth, and is of some gravity

as a general secondary infection may occur. As a rule abscesses heal rapidly after incision.

2. In the viscera: These are rare but have been noted in every organ. The brain, lung, heart, liver, spleen, pancreas and kidney have been involved. The ovary and tube may have abscess formation and perinephritic abscess has occurred.

3 In the glands: Any of these may be the seat of an abscess, especially the parotids, submaxillary glands, thyroid, breast and testicle.

4. In the abdominal cavity: Here there may be a great variety of curious abscesses. After perforation, especially in the ileocæcal region, adhesions may wall off the abscess cavity and perforation take place later into the bowel or externally. It is a question whether such abscesses may occur without perforation of the bowel but this seems possible. Subdiaphragmatic abscess is rare. In one patient with perforation and general peritonitis a large abscess was found between the right lobe of the liver and the diaphragm. It was difficult to say whether it had been due to the perforation. Abscess may follow suppuration in a mesenteric or retroperitoneal gland. Pelvic abscess may occur, either by extension from the tube or from perforation in the rectum. In one of this series a pelvic abscess was due to previous salpingitis.

Gangrene.—This is not a common condition. Keen collected 133 cases in his monograph. It is not necessarily found in severe attacks only, many of the reported instances having occurred during a mild course. The cases may be classed under the following heads: (1) Superficial gangrene of the skin, remarkable instances of which have been reported by Stahl, who saw a number at one time. (2) In association with bed-sores. This is usually due to pressure but in some cases apparently occurs in areas not especially exposed to this. It occurs rarely about the heels. (3) In association with conditions in the arteries. Plugging of the arteries may be due to embolism or thrombosis, the latter more frequently. The gangrene from this cause is of the dry variety and usually occurs in the extremities. (4) With venous thrombosis. This is rare, considering the frequency of thrombosis. The gangrene is of the moist variety. (5) A group of cases with gangrene occurring in various superficial areas, seen especially about the genitalia and perineum, especially in women. Other areas, as the lips, ears, tongue, uvula, etc., are sometimes involved. Noma has occurred rarely. There are a few instances of gangrene of the lung. An area of gangrene on the abdominal wall has followed the prolonged application of an ice-bag.

Gangrene occurs in the lower extremities in a considerable majority. Keen has laid emphasis on this as suggesting that the state of the circulation is an important factor. There is nothing distinctive about the symptoms of gangrene. Pain if present is usually due to an associated condition, such as thrombosis.

DURATION.

The length of the attack varies greatly and no definite period can ever be set. The average duration in the last 500 cases of this series was 29.4 days of fever and 49 days from the onset until discharge from the hospital (those with relapse or perforation and the fatal cases not being included). This does not represent the length of stay in the hospital but the time from the

onset of the disease, and the patient was not considered free of fever until the temperature was normal during the whole twenty-four hours. Among 73 patients with one or more relapses the average duration of fever in the original attack was 30.4 days and the average from onset until discharge from the hospital 73.2 days. It has never been the custom in the clinic to discharge the patients at the earliest time that they seemed able to go.

RECRUDESCENCE AND RELAPSE.

The term recrudescence is used here for periods of fever which do not last for more than a few days and are not accompanied by other signs, such as fresh rose spots. Return of fever due to a complication is not considered a recrudescence. A relapse must be characterized by at least two of the three important features of the disease, namely, a characteristic fever-curve, enlargement of the spleen, and rose spots. As a rule it is well to insist on an interval of twenty-four hours of normal temperature before the subsequent elevation, to justify a diagnosis of a true relapse. The term intercurrent relapse is used to describe those cases in which the temperature is dropping or has fallen perhaps nearly to normal and rises again, to remain elevated for some time.

Recrudescence.—The prominent feature is fever, which as a rule is not high and does not last for more than a week. The patient may feel just as well as before or complain of slight malaise and headache. The cause of these elevations may be excitement, too much exertion, solid food, constipation or a slight attack of diarrhœa. In some patients it has been coincident with the appearance of typhoid bacilli in the urine and careful search should always be made for this when an otherwise unexplained elevation of temperature occurs. In the last 685 cases there were 18 regarded as recrudescence and in 3 of these there was also a relapse. The average duration of fever was about one week. The longest interval of normal temperature before a recrudescence was sixty-two days.

Relapse.—This occurred in 172 patients in this series (11.4 per cent.). The figures given by different writers vary all the way from 3 to 15 per cent. and a collection of 28,057 cases showed 2,493 of relapse (8.8 per cent.).[1] The number varies from year to year and also in different localities. We can lay down no positive rule that a certain period of apyrexia must occur before the use of the term relapse is justified, for the general features must always be taken into consideration, and if the temperature has been steadily falling and almost normal for some time a sudden elevation of temperature with the other signs should be considered as the beginning of a relapse. In some cases it seems perfectly justified to make a diagnosis of relapse after only a few hours of apyrexia although usually there should be an interval of twenty-four hours of normal temperature. Relapses may be divided into the ordinary and intercurrent.

The Ordinary Relapse.—The average period of apyrexia between the original attack and the relapse is about 6 days and the longest interval in this series was 43 days. There seems little doubt that the predisposition to relapse is greater after a mild than after a severe primary attack and the

[1]Statistics of Curschmann, Gerhardt, Liebermeister, Murchison, Brand, Hare, J. McCrae, London Fever Hospital, and the present series.

mildest cases may be followed by a very severe relapse. After a severe primary attack a relapse is usually milder than the original. In some patients the diagnosis may be made only with the onset of the relapse, when rose spots may be seen or the Widal reaction given for the first time. The onset may be very sudden with a chill and high fever or with complications, such as orchitis, glossitis or phlebitis. Enlargement of the spleen seems to persist after defervescence in a large number of patients who later have a relapse. The pulse rate sometimes rises before the temperature. The symptoms do not differ especially from those of the primary attack, although as a rule the pulse is more rapid in the relapse, and dicrotism is said to be less common. Hemorrhage and perforation are apparently much less common in relapse, there being only 2 instances of hemorrhage and 1 of perforation among this series. As a rule the course is more favorable than in the original attack, for among 172 cases of relapse there were only 5 deaths (2.9 per cent.). Some statistics give higher figures but the mortality is usually low.

One group deserves special mention—that in which the duration of the relapse may be very long or more than one relapse occur. There are a number of instances with five relapses reported. In these protracted cases the duration of the disease may be almost a year, as in one of this series.

Intercurrent Relapse.—This is fairly common, although it may be difficult at times to say whether or not the diagnosis of intercurrent relapse is justified. We can usually make it when the temperature has been falling but is not down to normal and suddenly goes higher and continues elevated. These attacks may be protracted and severe and are responsible for many of the cases which drag on for months. The symptoms are not especially different from the ordinary attack, except that severe features may be present for a long period. The death-rate is usually higher than in the true relapse. In others there may be little but the fever, which sometimes seems as if it would continue indefinitely. At times a patient may have a moderate or even slight attack without high fever, and at the end of the third week the fever becomes higher and all the symptoms are more severe. It is doubtful whether such instances should be included under this term. In some patients, especially after a protracted course, the temperature may fall to normal and then for several weeks run along at about 100° to 101°, and with this there may be no special features. It is hardly correct to term this a relapse. Care should always be taken not to mistake a secondary infection for a relapse.

The explanations given for relapse are not very satisfactory. It may occur when the bactericidal power of the blood is highly developed and may be then due to certain strains of bacilli having greater resistance and so being able to multiply. But the whole matter is so involved with the difficult problems of immunity that many points must be left for future explanation. As Ewing points out, the occurrence of relapses in typhoid fever suggests that more than the bactericidal power of the blood or the neutralization of specific endotoxins is concerned. For a time it was regarded as a re-infection but this is contrary to the behavior of acute infections generally. The gall-bladder was considered to be a source of infection and the early giving of solid food, causing an increased flow of bile, was thought to explain certain instances in which the relapse seemed to be determined by dietetic errors. But this can no longer be regarded as satisfactory, especially when we

consider how frequently the bacilli must persist in the gall bladder, not to speak of other localities. The explanation that in relapse cases there is special involvement of the large intestine is not supported by autopsy records. Durham has suggested the most satisfactory explanation. Infection is the result of the action of a sum of a number of infecting agents which are similar but not identical, so that there may be a number of varieties and subvarieties. If the members belonging to different varieties are nearly equal we have a "normal or isozymic" infection, in which no unit predominates, each is affected equally by the anti-bodies, and no relapse results. However, if one variety predominates we have an "abnormal or anisozymic" infection and there may be but small protection against one form, which may begin to multiply rapidly and cause a second infection. In connection with this the finding of both the typhoid and paratyphoid bacillus in the one patient may be noted.

VARIETIES.

Different forms of the disease have been described and in some the most marked symptoms have been fixed on, so that such names as pneumotyphoid, nephrotyphoid, etc., came into use. It does not seem advisable to use these designations, as they lead to confusion. The symptoms in one system may be especially prominent at the onset and the same may occur during the course. It is convenient to separate certain varieties but it is to be understood that cases do not necessarily conform to any of these.

1. **Malignant Typhoid Fever.**—The mode of onset is usually very sudden with high fever early in the attack, or more gradual with severe prodromal symptoms. This variety seem likely to occur in young adults who are stout and well-nourished. From the onset the symptoms are severe and there is often marked toxæmia with signs of cardiac weakness. The patients sink into the characteristic typhoid state, the pulse becomes rapid and weak, distension of the abdomen occurs frequently, diarrhœa may be present, and the fatal termination may come before the end of the second week. Death is usually from severe toxæmia; hemorrhages may occur but are not common. In such fatal cases, at autopsy the intestinal lesions are usually not far advanced and their extent does not correspond to the severity of the clinical picture. The prognosis is exceedingly grave and from the onset the outlook is serious.

2. **Mild Typhoid Fever.**—This is an exceedingly important group, especially as regards prophylaxis, for these very mild attacks may not be recognized and the patients are the means of spreading the disease. Griesinger suggested the term typhus levissimus, while Brouardel proposed the name of typhoidette. The cases may be divided into two classes, the first including those characterized by a mild and short course, the other those in which, despite the short course, the onset is severe. To this latter group the term of *abortive* typhoid is often applied, for although the attack begins with severe manifestations, these suddenly disappear, the temperature soon falls, and the course is short. In many instances these mild forms are taken for other conditions, such as malarial fever, mountain fever, etc., while doubtless they are not uncommonly put down as febricula. In epidemics, certain patients may have slight fever, perhaps with some diarrhœa, lasting only for a few days.

The recognition of this group comes through one of two ways. They may show characteristic signs, such as rose spots, or be recognized only through the routine Widal reaction. In mild attacks the rose spots may not appear until after the temperature is normal, and if there has been no suspicion of typhoid fever it is not likely that careful search would be made for them after the fever has disappeared. Sometimes the diagnosis may be made only by a relapse or the appearance of some complication. The relapse is commonly more severe than the original attack. In other instances it may be the onset of phlebitis that suggests the diagnosis. Briggs studied the 44 cases of this series which could be put under the heading of "mild" and in which the fever lasted two weeks or less. Rose spots were present in 24, the Widal reaction was given in 26, and relapse occurred in 3 of the cases. The routine Widal reaction has been of great service in the recognition of this group; the older statistics cannot be regarded as being as accurate as those made since its employment. In the group with a sudden severe onset but a rapid defervescence the duration may be comparatively long and certain organs show marked involvement. Curschmann considers that the rose spots are more often absent than in the ordinary cases. These patients may show severe complications, such as hemorrhage or perforation.

We are not sufficiently impressed with the importance of this group. Keeping their frequency in mind, the physician will watch more closely and have the agglutination reaction tried more frequently in patients with mild fever. It is easy to use every means of diagnosis to clear up a doubtful severe infection or at any rate there is the stimulus to do so, whereas in a mild fever with rapid recovery and the patient well it requires energy and a strong sense of duty to do it. Even the patient may not appreciate what seems to him needless enthusiasm and care, still for him it may be a safeguard when we recall instances of a fatal relapse after a patient has returned to work, which gave the diagnosis with unfortunate certainty. For the community the recognition of this group is most important and many instances of infection are probably due to the mild unrecognized attacks. Their possibility should be especially kept in mind when the disease is prevalent and always in the case of children.

How mild may a typhoid infection be? During epidemics persons may complain of symptoms which persist only for a few days and there is the suspicion that such may be instances of very mild infection. The occurrence of typhoid bacilli in the stools of individuals who are apparently perfectly healthy is important in this connection. These mild attacks may be compared to those seen during an epidemic of cholera, in which infections of very varying severity were found. There are all grades from patients who have only a slight diarrhœa up to those with severe infections. Then, too, during an epidemic, cholera bacilli may be found in the stools of apparently healthy individuals.

3. **Ambulatory Typhoid Fever.**—This term is variously used and some confusion has arisen as to its meaning. It is sometimes applied when the symptoms are so mild that the patient hardly feels ill enough at any time to go to bed and may be at work throughout the entire attack. It is likely that a number of such cases are never recognized, as shown by the fact that patients who have kept at work throughout the original attack occasionally come in at what is evidently the beginning of a relapse. This type of case really belongs to the mild group. The other use of the term is to describe

the group in which the patients have fought the disease and kept about on their feet. This is seen especially among laborers, sailors, etc., but also in the higher walks of life and not uncommonly in physicians and nurses, who may keep at work for days with high fever. The course is usually exceedingly severe and often within a few hours after going to bed the patients become delirious and show marked nervous manifestations. In others, hemorrhage or perforation may be the first thing that makes them give up. One patient had kept at work until the onset of the severe abdominal pain which accompanied intestinal perforation. This group comprises many of the patients who take long journeys to their homes and in whom the death-rate is high.

4. **Hemorrhagic Typhoid Fever.**—This group comprises the cases in which bleeding occurs from various parts of the body. The term should not be applied to those with hemorrhage from the intestine only or to those with a petechial rash. It is rare and occurred in only 3 cases of this series, in 1 of which there were no intestinal lesions. Liebermeister noted it in 3 among 1,900 cases, and Uskins in 4 among 6,315 cases. Curschmann had seen 6 cases. It may be present in the malignant type, during the course of an ordinary attack, in the later stages or even in a relapse, as in one of our patients. The bleeding is frequently from the nose, gums and intestines and less often from the lungs, kidneys or uterus. Petechiæ frequently appear and may be seen between the rose spots, which do not necessarily become hemorrhagic. There may be bleeding into the tissues, and cerebral hemorrhage has occurred. In severe cases gangrene may follow. While the above description applies to the severer cases it is probable that the milder ones are not so rare as statistics indicate.

We are unable to give any explanation of the cause; in some it is analogous to the hemorrhagic cases seen in other infectious diseases. In others it may be associated with a secondary infection, especially of the pyogenic cocci, or it may be a cachectic manifestation. Rarely it may be due to the hemorrhagic diathesis or to the association of purpura hemorrhagica with typhoid fever. The coagulation time is prolonged. The outlook is grave and the majority of the patients die—about two-thirds of those reported—although all in this series recovered.

5. **Afebrile Typhoid Fever.**—This is described and while it is not possible to deny that it occurs, still the cases must be very rare. Some of those described in several recent articles had slight fever for some days and really belong to the group of mild cases. The majority of those reported were before the days of serum diagnosis. In debilitated and old persons an attack may occur without any fever. There was no instance in this series. There are certain possible sources of error, for patients with a very mild attack may come under observation with an enlarged spleen after the temperature has fallen to normal and rose spots may appear for the first time after this.

Variations Depending on Condition, Race and Age.—**Condition.**—Under this heading there are no positive facts to be considered, although the majority of physicians have certain ideas on the subject. As a rule fat patients do badly and we much prefer to have the lean type to deal with. Many believe that patients who have used alcohol freely are bad subjects. In regard to the station in life there does not seem to be any special difference between the upper and lower classes. In those who have suffered privation, the lack of care early in the disease is an important factor. There is an idea

very firmly fixed in the popular mind that those who have the disease were previously run down in health and so more subject to infection, but that there is any basis for this opinion seems very doubtful. It is certainly very common for patients to have been in excellent health before the onset.

Race.—This is of interest in localities where the colored race is present in large numbers. The ratio of colored to white patients with typhoid fever in this series is about the same as in the total medical admissions. The colored patient seems less resistant than the white. The death-rate in this series among the colored has been practically double that in the white (15 per cent. in the colored and 7.8 per cent. in the white). The colored patients seem to "go to pieces" more easily and if they have intestinal hemorrhage or severe toxæmia, especially with cardiac weakness, death may follow very rapidly, the outlook in these conditions in the colored being much worse than in the white. It has to be remembered that colored patients are likely to have had greater privation and less care before admission.

Sex.—No special difference is found as regards the sexes. The death-rate is about the same in large statistics. Men are more likely to keep about on their feet and be admitted with severer symptoms. Alcoholism is more common among them, while in the other sex pregnancy is the most important modifying factor, and if this be present the patients are exposed to somewhat greater risk.

Age.—This plays an important role. For the first two years of life the danger from typhoid fever is comparatively great, from two to fifteen there is much less risk, while after forty the danger is greater and increases with each year of life.

Typhoid Fever in Infancy.—Formerly regarded as rare, we have learned that typhoid fever during the first two years of life is not uncommon. The question has recently been studied by Griffith and Ostheimer, who collected 325 undoubted cases under the age of two and a half years. Of these, 111 were in the first year, not including the congenital cases, of which they found 12 undoubted instances and quote 5 doubtful ones. The presence of the Widal reaction is not sufficient proof of the correctness of the diagnosis of congenital typhoid fever, as the alggutination may have passed from the maternal to the fœtal blood through the placenta or after birth through the milk. Intestinal lesions appear to be rare in these cases. The death-rate is high and only 3 of the patients recovered. Of those in the first year recovery was noted in about 25 per cent. but it must be remembered that probably the diagnosis was not made in many instances of recovery. In the second year they found 171 genuine and 7 doubtful cases, with recovery in nearly 70 per cent. in which the result was given Of the cases in the first half of the third year 28 per cent. died. In their series the males and females were equal in number. More than half of the cases occurred during general or house epidemics. A paratyphoid infection has been found in infancy.

The symptoms in infancy show some variation from those in adult life. The onset is more variable and nervous features, which may suggest meningitis, are prominent. Rose spots and enlargement of the spleen are apparently as common as in adult life, while hemorrhage and perforation are comparatively rare, probably due to the slight development of the intestinal lesions, with less tendency to deep ulceration. The duration of the attack seems to be shorter than in adults. The mortality of the published cases is high but the milder cases are often overlooked or not reported. Serious conditions some-

times follow recovery, such as deaf-mutism, aphasia, convulsions and arrested mental developement.

Typhoid Fever in Childhood.—This offers no special features, except that as a rule the course is mild. The fever may not be high but the pulse rate is often more rapid in proportion than in adults. There are no special points of difference in the symptoms. Children are very apt to pick at the nose and lips, so that fissures and bleeding often occur. Distension of the abdomen is not uncommon but hemorrhage is comparatively rare. In very young children the symptoms may be much like those of colitis. The majority of writers state that perforation is very rare in children but such is not the experience in this series, as among 40 cases of perforation there were 4 in children under fifteen years of age. Children seem to do very well after operation for perforation, 3 out of the 4 recovering. Among the complications and sequelæ, aphasia, mental changes, otitis and bone lesions are apparently more common than in adults. The duration of the fever is generally less than in adults and the mortality is less. Children are said to be more subject to relapse than adults.

Typhoid Fever in the Aged.—After forty, typhoid fever is much more serious and the mortality is high. As a rule, in advanced life the features are not so acute as at earlier periods. The patients are likely to show early delirium, usually of a low type, the temperature is not so high and often remittent. Frequently the pulse is rapid and cardiac weakness appears at an early stage. Severe bronchitis, bronchopneumonia and hypostatic congestion are common. Enlargement of the spleen may not be evident; hemorrhage is exceedingly grave in advanced life. If recovery follows, the convalescence is likely to be slow and protracted.

Typhoid Fever in Pregnancy.—The association is not very common and in this series among 438 female patients 6 were pregnant (1.3 per cent.), 5 of whom aborted. Considerable difference of opinion exists as to whether pregnancy gives a relative immunity against infection with the typhoid bacillus; certainly during the puerperium and lactation typhoid fever is comparatively rare. Abortion may occur comparatively early in the disease but in one of our patients it did not occur until convalescence. While adding somewhat to the risk, pregnancy with typhoid fever can not be considered as being very serious. An attack during lactation does not show any special features. One patient admitted in the second week of a severe attack had nursed her child up to the time of admission; he had suffered from diarrhœa, which disappeared as soon as nursing was stopped, but his blood did not give a Widal reaction. There are some cases of puerperal infection due to the typhoid bacillus. There have been 3 of these in the obstetrical department of the Johns Hopkins Hospital. One showed a localized lesion in the chorion from which typhoid bacilli were obtained.

Typhoid Fever in the Fœtus.—In a certain number of cases there is intra-uterine infection; the fœtus shows a septicæmia without internal lesions. This is not invariable, as there are instances in which the child escaped, as in some of this series in which the Widal reaction was not given by the blood of the fœtus and cultures were negative. The conditions which determine the passage of the bacilli from the maternal to the fœtal circulation are not positively known but probably some disease of the placenta is necessary, and hemorrhagic infarcts have been found in several cases. When the fœtus becomes infected death follows in the majority of cases but this is not

invariable. The presence of bacilli must be proved before a diagnosis is made.

"Colon Typhoid."—Some writers have drawn attention to a group of symptoms found when the colon is specially involved. These comprise a fœtid diarrhœa, marked meteorism, frequent hemorrhages, small in amount and of bright red blood, and a rapid downward course.

Paratyphoid Fever.—Some would separate the diseases due to the paratyphoid and paracolon bacilli into one or two distinct groups, terming all paratyphoid or paratyphoid and paracolon depending on the organism. Epidemics of paratyphoid fever have occurred from infection conveyed by meat. At present it seems better to consider them all under the heading of "Typhoid fever" but further experience may prove the other method to be better. The general features of these infections show some difference. Fox[1] has recently reviewed the subject. They may be divided into two groups, A and B, with a relative frequency of 1 to 5. Some of the latter are much like the infections with *B. enteritidis*. Fox considers that paratyphoid fever has a shorter period of invasion, fever, and total duration. The fever shows more marked remissions. Group A is more like typhoid fever than B, which resembles septicæmia with a tendency in the complications to be more numerous, purulent and fulminating. The range is described as being from subacute typhoid to severe acute meat poisoning. Practically all the conditions found in typhoid fever may occur with these infections. Reference has been made to an instance of typhoid spondylitis and bony deposits with a "paracolon" infection. The diagnosis of this group can only be made by positive blood cultures. The serum reaction is not sufficient.

ASSOCIATION OF TYPHOID FEVER WITH OTHER DISEASES.

This is rare when we consider the number of possible combinations, and when acute infections occur together it is rare that one of these is typhoid fever.

Malarial Fever.—Perhaps the most important association is that of malarial and typhoid fevers, not for their actual co-existence but on account of the ideas as to the frequency which have existed in the minds of so many of the profession in this country. "Typhomalarial" or "malarial typhoid fever" is the diagnosis most frequently made of continued fever in some sections of the country. Three conditions are included under the term. (*a*) It is applied to patients with malarial fever who are in the "typhoid" state or who have a very severe infection. (*b*) A hybrid disease, formed by the union of malarial and typhoid fevers. This disease, non-existent in the patient, still finds an abode in the minds of many of the profession. This was the sense in which the term was used by Woodward, who introduced it in 1862. (*c*) The occurrence of the two diseases in the patient at the same time, which is the sense in which the term has been used by French writers especially. A fourth class might almost be added, owing to the habit many physicians have of diagnosing many obscure febrile affections as "typhomalarial" fever. It is to be hoped that the profession will cease to use the term and much can be done by boards of health refusing to accept it as a

[1] *University of Pennsylvania Medical Bulletin*, vol. xviii, 1905.

cause of death. In mortality returns "typhomalarial" fever may be considered as practically always typhoid fever.

The actual association of typhoid and malarial fevers is rare. Lyon, who carefully studied the reported cases in 1900, found only 30 undoubted instances. Craig, among 5,000 patients with malarial fever, found only 8 with typhoid fever. In the report of the Spanish-American War Commission the total number of cases is put at 95. Among these, malarial fever in 3 preceded the typhoid attack, in 2 both preceded and occurred during convalescence, in 18 was at the beginning of the typhoid attack, in 12 was co-incident, in 52 during convalescence, in 3 two to six months after the typhoid attack, in 4 undetermined, and 1 was found at autopsy. The infections were co-incident in 12 cases only, and it is noted that some of these were open to criticism. In 44 cases where the organism was determined, tertian was found in 22, æstivo-autumnal in 12, quartan in one, and in 12 there was a combined infection. There were 15 deaths among the 95 patients. In this series there were only 3 instances of combined infection. When the reported cases are studied it is seen that the mlaarial parasites were found in the blood during the fever of the typhoid attack in a very small number. In a large majority they appeared during convalescence, exactly as they may after a surgical operation or confinement if there has been a previous malarial infection.

Tuberculosis.—This association is of interest in many ways. Does typhoid fever predispose to tuberculosis subsequently? Does tuberculosis give a relative immunity against typhoid fever? This is difficult to decide by statistics, but when we remember the large number of individuals with tuberculosis the percentage who have typhoid fever seems small. The association may be considered as follows:

1. They may co-exist and a patient with tuberculosis have typhoid fever. In this series a clinical diagnosis of pulmonary tuberculosis was made in 6 patients and at autopsy active tuberculosis was found in 7 cases, of which 2 were in the lung and 5 in the glands. One of the patients with tuberculosis of the mesenteric and bronchial glands had also a tuberculous meningitis, and one with involvement of the bronchial glands had Addison's disease. In one patient the caseous bronchial glands had perforated into the trachea and one bronchus. Evidence of old tuberculosis was found at autopsy in 9 instances, of which 5 were healed lung lesions and 4 chronic pleurisy. There are instances of fatal pulmonary hemorrhage during the attack of typhoid fever. One patient of this series had a sharp pulmonary hemorrhage which had no marked effect on the condition. Miliary tuberculosis and typhoid fever may co-exist, as in a series of cases recently reported by Anders, but these are rare. The occurrence of typhoid fever and tuberculous meningitis is very rare. There was one instance in this series of glandular and meningeal tuberculosis with typhoid fever. The patient went through a severe attack of typhoid fever and after five days of normal temperature meningeal symptoms began, death occurring three weeks later.

2. Tuberculosis may follow typhoid fever. By some writers this is regarded as being by no means rare, but it seems more probable that in the majority the diagnosis of typhoid fever was wrong and the condition tuberculous from the beginning. In some patients a previously existing focus may be stimulated to greater activity, as is probably most common in glandular tuberculosis.

3. The diseases may be mistaken for each other. This is probably the most frequent association, one disease in the patient and the other in the mind of the physician. There are several forms which may lead to confusion.

(*a*) *Acute Miliary Tuberculosis.*—This mistake may be made even with the possibility of it in mind. As a rule the error is in mistaking miliary tuberculosis for typhoid fever rather than the reverse.

(*b*) *Tuberculous Meningitis.*—This may show symptoms suggestive of typhoid fever, especially if the patient is not seen from the onset, but the absence of the characteristic signs of typhoid fever and the results of lumbar puncture should give the diagnosis.

(*c*) *Tuberculous Peritonitis.*—If the patient has been seen from the beginning there is rarely confusion, but later, especially if the history be indefinite, they may be difficult to distinguish.

(*d*) *Glandular Tuberculosis.*—If this be accompanied by constant fever and toxæmia the diagnosis may be very difficult.

(*e*) *Pulmonary Tuberculosis.*—If the fever be constant and toxæmia marked there may be confusion, but a careful examination of the lungs should render the mistake unlikely.

In all of these a tuberculous condition is usually regarded as typhoid fever but the contrary mistake may be made, perhaps most commonly in patients whose attack begins with marked pulmonary or pleural signs. When meningeal symptoms are prominent early in the disease the diagnosis of tuberculous meningitis may be made.

Acute Infections.—The coincidence of these with typhoid fever is relatively rare. As regards scarlet fever, Fournier in a recent review of the literature found 75 instances of the co-existence of this with typhoid fever. Typhoid fever may precede, which is the most common association; the diseases may occur together, as in an instance reported by Hektoen; or typhoid fever may occur after the attack of scarlet fever, as in the report by Bloch of an epidemic in a scarlet fever pavilion (there were 13 patients and in all a gonococcus infection was present also). Murchison noted instances of double infection when patients with different acute contagious diseases were treated in the same wards. Caiger among 48,000 scarlet fever patients in the London Fever Hospitals reports 11 as having typhoid fever associated. The prognosis of the typhoid fever does not seem any worse on account of the association. Smallpox, measles, chickenpox and whooping-cough have been observed, usually coming on in the latter part of the attack of typhoid fever. Typhus fever has followed the other disease, instances having been noted where a patient with typhoid fever has been sent to typhus wards and contracted the disease. Before the diseases were separated this must have occurred frequently. Diphtheria may be seen in its usual form or, as in one of this series, there may be a diphtheritic membrane on the lips (from which the Klebs-Loeffler bacillus was obtained) without throat involvement. The presence of the diphtheria bacillus is necessary for diagnosis, as a diphtheroid membrane may occur in typhoid fever. Some cases of co-incident infection with the *B. typhosus* and streptococci have been reported, both typhoid bacilli and streptococci being found in blood cultures. These are usually very severe and run a rapid downward course. They are to be distinguished from instances of secondary infection late in the attack of typhoid fever Influenza and typhoid fever may co-exist; they may run concurrently or the influenza may precede the typhoid attack. In some cases a severe influenza

infection may simulate typhoid fever. Erysipelas is not common. Among 1,635 cases of erysipelas, Anders found 2 associated with typhoid fever. It may occur during the height of the disease or in convalescence; the occurrence of bed-sores or boils probably favors its appearance. Asiatic cholera and typhoid fever have been associated but usually one disease follows the other. Tetanus and anthrax have occurred with typhoid fever. Gonorrhœa and typhoid fever may co-exist.

Gastro-intestinal Disease.—The occurrence of gastro-intestinal disorders apparently does not predispose to typhoid infection. Typhoid fever may occur in patients who have amœbic dysentery and Strong found 4 cases among 100 fatal cases of amœbic dysentery in Manila. During the attack of typhoid fever the amœbæ may not be found in the stools but reappear in convalescence. One patient of this series entered the hospital for amœbic dysentery and was found to have typhoid fever. The attack was uneventful but in convalescence an amœbic abscess of the liver developed. He recovered after operation. The severe intestinal features of typhoid fever, especially if there be extensive ulceration of the colon, may suggest dysentery, but the diagnosis should be made only if amœbæ or *B. dysenteriæ* are found.

Trichinosis.—Until 1862 these diseases were always confounded. There was one instance in this series of their association. Trichinosis may simulate typhoid fever very closely, as the general features, enlarged spleen, rose spots—although they do not come out in successive crops—and diazo reaction may all be present.

Chronic Diseases.—It has been thought that chronic nervous diseases and typhoid fever rarely co-exist but this is probably not correct. Patients who have epilepsy usually have fewer attacks during the course of the fever. In patients with chorea the movements usually stop during the attack but may recur in convalescence. In some instances the choreic movements have been much exaggerated at the onset of the attack. Patients with hysteria or neurasthenia who have typhoid fever are often markedly benefited. In a patient with diabetes mellitus the excretion of sugar may diminish markedly or even disappear during the attack. The association is usually regarded as having a grave prognosis and Curschmann points out that the temperature in these patients is often comparatively low. In one patient diabetes mellitus appeared six months after the attack of typhoid fever and another returned within a year with diabetes insipidus. Typhoid fever may develop in a patient with cholelithiasis and a greater likelihood of cholecystitis might be expected. In 4 of this series, gall stones were found at autopsy, in 2 being associated with malignant disease.

Malignant Disease.—Typhoid fever rarely develops in patients who have malignant disease and the difference in the ages of greatest incidence does not altogether account for this. In this series it occurred in 2 instances, one being carcinoma and the other sarcoma of the gall bladder. In both the infection with the *B. typhosus* was apparently a terminal one.

Syphilis.—This association is not rare and a number of cases are scattered through the literature. Some of the physicians in the South African War considered that in patients with syphilis who contracted typhoid fever the outlook was grave and the death-rate high.

Chronic Alcoholism.—Chronic alcoholics are usually bad subjects and show a very high mortality. They have slight resistance and are prone to serious cardiac manifestations, also being apt to show marked nervous mani-

festations with low delirium, marked restlessness and great prostration. Active delirium tremens does not seem to be very common in typhoid fever. Curschmann considers that alcoholics are especially apt to have severe hemorrhages and are also more liable to renal complications.

Appendicitis.—The relation of this condition to typhoid fever is an important one.

1. One may be mistaken for the other. This is by no means infrequent; usually the patient with typhoid fever is thought to have appendicitis. Abdominal pain, especially in the right iliac fossa, is by no means rare at the onset of typhoid fever, and if this have come on acutely the mistake is easily made. There may be tenderness on pressure, but if the patient is carefully examined and especially if pain, rigidity and muscle spasm are usually regarded as necessary signs of appendicitis, there will be fewer mistakes. The leukocyte count is valuable, as in typhoid fever it is usually low and in appendicitis (apart from the instances of general peritonitis, which are usually readily recognized) there is likely to be leukocytosis. The thorough routine examination of the patient is of much help. In case of doubt, waiting and careful observation will usually give the correct diagnosis within twenty-four hours.

The mistake of considering appendicitis to be typhoid fever is not likely if the patient has been seen from the onset but is possible if he is seen for the first time after an illness of some days especially if there be a small abscess. However, in the great majority of such cases, careful examination should give the diagnosis without doubt.

2. Conditions in the appendix due to the specific typhoid lesions. The occurrence of ulceration in the appendix is comparatively common. It was found in 19 out of 105 cases at autopsy and 3 others showed swelling of the mucous membrane. It is easy to understand that with these lesions we may have acute symptoms but still, considering their number, appendicitis is comparatively rare. In some instances the attack of typhoid fever may be associated with changes in the appendix from previous inflammation, of which 4 were found at autopsy. Changes secondary to the typhoid lesions may occur.

3. *Perforation.*—This may occur in the appendix as elsewhere and requires no special discussion. The symptoms do not vary from those ordinarily found in perforation elsewhere. It is possible that perforation occurring in an appendix which is lying posteriorly is more apt to be walled off and cause a local abscess.

4. *Acute Appendicitis with Typhoid Fever.*—This is comparatively rare but does occur There was one such instance in this series, the appendix being found acutely inflamed but without any evidence that this was associated with a typhoid lesion.

5. *Appendicitis May Follow Typhoid Fever.*—This may be an accidental association or following the typhoid ulceration subsequent inflammatory changes may be favored.

Intussusception.—Several instances of this have been reported, in one with hemorrhage, the diagnosis of perforation being made. Intestinal obstruction due to various causes may occur.

Associated Bacterial Infections.—These may be various. Thus infection with the pneumococcus and typhoid bacillus is usually present when pneumonia is a complication. Both organisms have been obtained in

blood cultures. The influenza bacillus may be obtained in the same way. Of the pyogenic organisms, streptococci may be associated early in the attack or streptococci or staphylococci later, sometimes from infection from bedsores or boils. These however are rather secondary than co-incident infections. In some instances typhoid and paratyphoid bacilli have been obtained from the same patient.

CHAPTER V.

THE DIAGNOSIS AND PROGNOSIS OF TYPHOID FEVER.

By THOMAS McCRAE, M. D.

"The diagnosis of this disease, during the first day or two, is extremely difficult, its character being simulated by different febrile and inflammatory affections."—JACOB BIGELOW.

THE diagnosis has to be made from the clinical features or by laboratory methods. With a disease which shows so many variations in its symptoms and course it is evident that diagnosis by clinical methods may be very difficult and it may be made only at autopsy. There is no symptom or sign which is invariably present, and although fever may be said to be of almost constant occurrence, yet this may be of slight degree or more or less irregular. There are some general statements which may be made. Other diseases simulate typhoid fever more frequently than it simulates them, except when symptoms or signs are localized in one organ, as the "pneumotyphoid" variety. A good rule is to consider typhoid fever as a possibility in every doubtful condition associated with fever, even if this be somewhat irregular. Again, the relative frequency of diseases is an important point to be kept in mind. Typhoid fever is one of the most frequent continued fevers and if it be kept in mind as a strong possibility, the chances of overlooking it will be much less. Lastly, it is well to keep in mind that it may not be possible to make a correct diagnosis even under the best conditions. The number of patients in whom the diagnosis is made possible only by the occurrence of a relapse is a good example of this. In a doubtful case we must remember that it may not be possible to make a diagnosis for some time; the necessary data perhaps cannot be obtained.

The onset of typhoid fever is usually gradual. The patients can often tell quite definitely when the feelings of malaise first became marked, but after this there is rarely any change. In a small number the onset is sudden. The features of onset show no special peculiarity; general malaise, anorexia and headache are common. The face often has a characteristic heavy, dull expression and the patient may show a suggestive slow mental condition. He answers questions only after an interval and at first has difficulty in remembering the history of his illness, although after a few minutes he is able to answer all questions intelligently. As a rule there is fever when the patient comes under observation, although for some days this may be very slight and perhaps only after a week rises to the usual height. The occurrence of bronchitis is very suggestive; it varies greatly in severity and sometimes has distinctive features, the patient usually makes little complaint of it and while the cough may be severe there is rarely much sputum. The history of epistaxis is an important aid. The pulse may show two distinctive conditions, one dicrotism, which if found early is very suggestive, and the other a rate relatively much slower than that which might have been expected from the

degree of fever. With this there is a furred tongue which shows tremor early and perhaps a heavy, foul odor to the breath. The bowels may be constipated or there may be diarrhœa, especially if a purgative has been taken, and if so the character of the stools may be suggestive. In the examination of the abdomen, enlargement of the spleen is important, although it is often present in other acute febrile conditions, especially influenza. The presence of rose spots is the most important point and these should be looked for every day, it being kept in mind that they may be found only on the lower thorax or on the back, for it is by no means uncommon to find one or two spots on the back before they are present on the abdomen. There is often difficulty in determining whether doubtful spots are typhoid rose spots or not. In such cases it is well to mark a doubtful area and watch it during the next two or three days, when a decision should be easy. Abdominal distension is rarely present in the early stages of the disease. There is often slight tenderness in the right iliac fossa and gurgling is frequently obtained on pressure but there is nothing characteristic in either of these. Retention of urine early in the attack may be suggestive. In rare cases there is a characteristic musty odor but this is rarely of much aid.

The course of the fever in ordinary attacks is usually characteristic, as it is constant and rarely shows much variation. This is not always true and there may be a very irregular temperature curve, either early in the course or toward the end. If this be associated with chills the diagnosis may be difficult. If the diagnosis has not been made during the attack a temperature persistently below normal during convalescence from an illness with fever is always suggestive. The blood may not show any characteristic condition, although as a rule the number of leukocytes is below normal. A patient with fever and a leukocytosis certainly has not uncomplicated typhoid fever, so that, excluding a complication, an increase in the leukocytes suggests some other disease. In certain cases the differential count is of value even early in the attack, the especial point being an increase in the mononuclear elements, especially in the larger forms, and a decrease in the polymorphonuclears and eosinophiles. This may be quite marked later on in the disease as well. The urine may show the diazo reaction but less importance is now given to this sign. If internal hydrotherapy be a systematic method of treatment in febrile cases, a typical diazo reaction will not be obtained very often.

There are certain occurrences during the course of a doubtful fever which are important aids. Among these is the sudden appearance of deafness without any purulent process and the complaint of tender toes. The occurrence of hemorrhage or of perforation of the intestine is of course characteristic, while the onset of a phlebitis may clear up a doubtful attack. There are certain things which speak against typhoid fever such as herpes, coryza and conjunctivitis. Sweating during the height of the disease is rare, although it may occur at the onset, with certain complications, or during convalescence. Jaundice is rare, apart from gall bladder conditions. The blood count is important, any increase in the number of leukocytes being strongly against uncomplicated typhoid fever.

The laboratory methods of diagnosis are dependent upon the demonstration of the typhoid bacillus in the body of the patient, or obtaining the specific reaction with the blood serum. The greatest advances in diagnosis in recent years have been through bacteriology. The positive findings are as follows:

1. **Isolation of Typhoid Bacilli from the Blood.**[1]—This is comparatively easy of application with proper training, does not give the patient much discomfort, and very often gives valuable results as blood cultures may be positive, weeks before a Widal reaction is given. Thus in 16 cases among the last 500 of this series the typhoid bacillus was grown from the blood before any Widal reaction was given.

The greatest value of blood cultures is in the diagnosis of the cases with marked fever and perhaps no other positive sign. The bacilli are most frequently found in the blood early in the attack, perhaps before the usual signs of the disease, but later in the course they are not found so frequently and a negative result should not be given too much weight after some weeks of fever. This renders it important not to delay the taking of blood cultures in a doubtful case, as in typhoid fever each day's delay lessens the chance of a positive result. It also explains the value of blood cultures in the early recognition of the acute "septic" cases.

2. **Isolation of Typhoid Bacilli from the Stools.**—Much work has been spent in the attempt to perfect a practical cultural method, but heretofore many of these have apparently not been very reliable. Recently a very satisfactory one, known as the Drigalski-Conradi, has been devised, and with it a very large proportion of positive results are obtained. It has been extensively used in the campaign against typhoid fever in Germany. Probably with repeated examinations bacilli can be found in the stools of about 75 per cent. of the cases; cultures should be made immediately after the stool is passed.

3. **Isolation of Typhoid Bacilli from the Urine.**—In some instances this may be done before a positive Widal reaction is given, so that in a doubtful case the urine should be carefully examined and cultures made from it. In some instances it may be possible to recognize typhoid bacilli in the urine by its gross appearance; thus in a test-tube or specimen glass there is a curious shimmer when the urine is held between the observer and the light. The finding of actively motile bacilli in a specimen of urine recently passed is always suspicious. Cultures should be taken with great care to avoid contamination and in identifying the organism the frequent occurrence of the colon bacillus must be remembered. Typhoid bacilli rarely occur in the urine before the end of the third week, so that this is not an aid in early diagnosis.

4. **Isolation of Typhoid Bacilli from the Rose Spots.**—Cultures from

[1]The general method of making blood cultures is described on page 660, and special points are discussed in works on laboratory methods. A new method for the isolation of typhoid bacilli from the blood has been devised by Cole, Davidson, and Cronk The theoretical advantage of the use of large quantities of bouillon, and, in this way, the high dilution of the blood, is that by these means the bactericidal power of the blood is overcome. The attempt to overcome this antagonistic influence has been met by the addition of typhoid bacilli killed by heating, or the filtrate from typhoid cultures after autolysis. Wright and others have shown that the specific amboceptors are absorbed by such dead bacilli or their receptors. The practical application of this principle has led to the isolation of typhoid bacilli from the blood in about 70 per cent. of the cases. Only one cubic centimeter of blood is required, and this may be very easily obtained in a hypodermic syringe and added to about 10 cc. of the media. This greatly simplifies the use of blood cultures, and therefore adds very materially to its general application in diagnosis.

The addition of bile to the culture medium, as suggested by Conradi, does not seem to be of special value.

the rose spots yield positive results in the majority of cases but it is not a method available for routine clinical work, as it causes discomfort and as a rule there is little doubt of the diagnosis when typical rose spots are present. Blood cultures are as easily made and quite as satisfactory.

5. **Isolation of Typhoid Bacilli from the Spleen.**—This is done by puncturing the spleen and making cultures from the fluid obtained. The splenic dulness is carefully outlined and the puncture usually made in the eighth or ninth interspace about in the midaxillary line. At the time of puncture the patient should not breathe and it is well to have an assistant hold the thorax firmly with his hands. Usually only a few drops of fluid are obtained and with these cultures are made in bouillon. If positive the diagnosis may be made in ten to twenty hours. Adler reports this procedure in 300 cases and considers that positive results can be obtained in about 95 per cent. early in the attack, while later the results are often negative. Gabritschewsky reported 109 punctures of the spleen without any bad results. While this may be done in a large number of patients without any danger, yet there is always the chance of causing rupture of the spleen, and while this does not often happen, yet it seems to be a serious objection against this method. Adler also reports puncture of the liver in 4 patients, with negative cultural results.

6. **Isolation of Typhoid Bacilli from the Spinal Fluid.**—This is of especial value in patients admitted in delirium or stupor or with other severe nervous manifestations. The procedure is simple, lumbar puncture being done in the ordinary way and cultures made from the fluid obtained. The presence of actively motile bacilli in the fluid is suggestive of typhoid fever. It has to be borne in mind that typhoid bacilli may be found in the spinal fluid without meningitis being present.

7. **The Agglutination Phenomenon.**—Through the action of the bacteria on the tissues, soluble bodies known as agglutinins are produced in the blood, which when sufficiently concentrated have the property of clumping and rendering non-motile the specific organism whose activity gave rise to their production. To the agglutination phenomenon which occurs in typhoid fever the name of the Gruber-Widal reaction is given. The technique is as follows: A standard stock culture of the *B. typhosus* should be kept and an organism cultivated through many generations on artificial media is preferred. From this stock culture fresh cultures are grown on agar from twelve to twenty-four hours for use in the test. Some prefer comparatively fresh (ten to eighteen hour) bouillon cultures, while others use bouillon cultures killed by the addition of carbolic acid, formalin, etc. Hastings has devised a method which yields satisfactory and stable killed cultures. The organisms scraped from two twenty-four hour agar slant cultures of the *B. typhosus* are added to a mixture of: 5 per cent. aqueous carbolic acid 5 cc., glycerine 10 cc. and sterile 0.8 per cent. sodium chloride solution 85 cc. The material should be gradually and carefully rubbed into the solution with a small spatula and the mixture allowed to stand for five or six days before using. This is mixed with an equal volume of the diluted serum for the test. Living fluid cultures may cause confusion by the presence of clumps due to the growth of the organism, while of the dead cultures those killed with weak carbolic solution are preferred, as formalin may cause precipitation of proteids from the serum.

If a fresh culture is used for the test, rather dry slants on agar are best and the material may be emulsified in sterile salt solution (0.8 per cent.) or in bouillon. A loop full of the growth is rubbed against the side of the tube of salt solution until it is thoroughly broken up and then it is gradually mixed with the fluid. The size of the loop gives a fair quantitative measurement of the amount of culture used and the obtaining of a suspension free from clumps should be easy.

Collecting the Serum.—Glass tubes two inches in length by one-quarter inch in diameter are drawn out into a capillary tube at both ends. From a free flowing puncture in the ear or finger tip the blood is drawn by capillary attraction into the tube until it is about two-thirds full. The tube should then be kept flat until the blood has clotted and the serum separated from the coagulum. The tube is then filed and broken at a point just beyond the clot and the serum withdrawn by a capillary pipette. The process may be hastened and the amount of serum increased by sealing the end of the tube which is free from blood and centrifugalizing for a few minutes. If it is desired to preserve the specimen or to send it away, both ends of the tube may be sealed. Serum is best kept, after separation from the corpuscles, in a sterile tube. If larger amounts of blood are required this should be obtained from a vein. The serum may be obtained by blisters produced by the application of cantharides plaster to the skin and a sufficient amount can be got from a small one.

Diluting the Serum.—For this there are a number of methods. A piece of glass tubing one-quarter inch in diameter is drawn into a long capillary tube, which is plunged into the serum in the collecting tube and allowed to fill, care being taken to avoid disturbance of the corpuscles. From this tube the serum is dropped into the tubes or dishes in which the dilutions are made, salt cellars, watch crystals or small porcelain dishes being used for this. As a routine at least two dilutions of each serum may be made, of a ratio of 1 to 10 and 1 to 50. The procedure is as follows: To the first drop of serum add 4 drops of 0.8 per cent. salt solution, dropped from the same pipette which has been washed with distilled water and then dried in the flame. To the second drop of serum 24 drops of salt solution are added. This gives dilutions of 1 to 5 and 1 to 25. The additions of these solutions to an equal volume of the suspension of the typhoid culture gives a dilution of 1 to 10 and 1 to 50, and in the same way any other desired dilution may be made. If greater accuracy or very high dilutions be desired, especial mixing pipettes, such as those used for blood counting, may be employed, and these dilutions may be made directly from the whole blood with a pipette, using salt solution as the diluting fluid. In this method two volumes of blood should be considered as equal to one volume of serum. The mixture is allowed to settle or is centrifugalized.

There are two principal methods of making the test, the macroscopic and the microscopic.

1. **Macroscopic Method.**—This depends on the agglutination of the organisms into clumps which are visible to the naked eye and, later, the precipitation of these clumps, leaving a clear, supernatent fluid. The serum is diluted in a test-tube of small caliber and the organisms added either as a suspension of living or killed cultures. It may be more convenient to make the full dilution of 1 to 50 or 1 to 100 with salt solution, and then the organisms from a solid culture are suspended directly in this diluted serum as

described before. The tube is then examined by strong transmitted light to see that its contents are homogeneous and free from accidental clumps. A narrow band of light from a lamp enclosed by a screen aids in detecting the early appearance of clumping. The reaction is considered positive if there be general clumping with the dilution of 1 to 50 or higher in one hour, and complete precipitation leaving a clear, supernatent fluid after twenty-four hours. The reaction is hastened if the tubes are placed in the thermostat.

This method has the advantage of simplicity; no microscope is required and killed cultures may be used, which obviates the need of a thermostat and culture media. The "typhus diagnosticum" of Ficker, now so widely used in Germany, is a preparation of killed cultures, the formula for which is kept secret. Several laboratories in this country now make and sell killed cultures for this macroscopic method.

2. **Microscopic Method.**—The diluted serum is mixed with the required amount of the typhoid suspension as described above, and a drop of the mixture is placed on a hanging drop slide for observation. Some prefer to mix the two dilutions directly on the cover-slip, and for this a platinum loop of stiff wire is used, the plane of the loop being at right angles to the handle and its diameter being constant. The loop is dipped vertically into the serum dilution and the drop thus obtained is placed in the centre of the cover-slip. The loop is then passed through a flame and dipped into the typhoid suspension in the same way. The two drops are then thoroughly mixed in the cover-slip. This simple method secures approximately equal volumes and any desired dilution can be made. The cover-slip is then inverted over the well of a hanging drop slide which has been ringed about with olive oil or vaseline. The hanging drop is then examined with a moderately high dry lens and is best seen by artificial light, the diaphragm being adjusted so as to bring out the refractility of the bacteria.

The freshly made hanging drop should be free from clumps and show the organisms actively swimming about in addition to their Brownian motion. After an hour, if the test is positive, the organisms will be seen to be collected in clumps and to have lost their motility. The presence of two or three organisms in a field which otherwise shows good clumping does not prevent the test being considered as positive. Sometimes clumping is better at the higher dilution, while there may be marked bacteriolysis at dilutions of 1 to 10 or 1 to 20. Many normal sera give good agglutination at 1 to 10 but show no trace of reaction at 1 to 50, and therefore tests based on the low dilutions alone are unreliable.

The macroscopic method has rapidly gained favor and is perhaps less open to error than the microscopic, provided that strict limits of time and dilution are observed (one hour at a dilution of 1 to 50 or higher). A great objection to the microscopic method has been the different standard set by various observers, for some regard any segregation of a few organisms as a positive reaction, while others insist on clumping of all the organisms before the reaction is considered positive. These differences have led to much confusion.

Agglutination with Dry Blood.—The recommendation of this method, which was introduced by the late Wyatt Johnston of Montreal, is its convenience. The blood is obtained on a piece of glass, tinfoil or glazed paper, and even blotting paper has been used. Care must be taken to dilute the blood sufficiently in this method, which, while it may do for rather rough and

ready work, is thoroughly accurate only when the blood is weighed and the dilution based on the weight instead of the volume.

Diagnostic Value.—While the Widal reaction is almost always found at some period in typhoid fever, its appearance may be long delayed and it is rarely found before the seventh or eighth day. The persistence of the reaction is very variable, being from a few weeks to many years. Some instances of long persistence have been attributed to the presence of typhoid bacilli in the gall bladder or in the urinary bladder. The agglutination of *B. typhosus* by normal sera at the standard dilution of 1 to 50 in one hour is so rare as to be of little importance in diagnosis. The tears and sweat may give the reaction.

The question of associated alggutination, in which a serum agglutinates two or more closely related organisms, is of little practical importance. As a general rule, if the agglutination test is done with a high dilution and a reaction within a limited time demanded (1 to 50 in one hour), we may expect to have reasonably specific results. If there be an infection with organisms of the paratyphoid group, a positive diagnosis should not be made from the serum test alone but by means of blood cultures, as the possibility of the presence of associated agglutinins has to be kept in mind. A bacillus agglutinated by the patient's serum is not necessarily the causative agent of the disease, but this has to be regarded as strong presumptive evidence that it is.

In practical work the Widal reaction has a varying value. In one patient a positive result may give a diagnosis which otherwise might never have been made, while in another patient with undoubted signs of typhoid fever it may not be given until long after the temperature becomes normal. In a large series the number of positive results is high and should be over 95 per cent. The importance of testing the blood during convalescence must be remembered, as in several of this series the reaction was given only on the day of discharge. In others it may be obtained only in a relapse. In comparing the results of different observers it is necessary to consider carefully the technique as regards dilution, time, etc. The Widal reaction may be given in jaundice and it has been suggested that the antibodies may be formed by the irritation of the bile. Two instances of Weil's disease with a positive Widal reaction are reported, which is interesting in connection with the idea that this disease may be a typhoid infection.

It seems fair to consider that the Widal reaction is of great value when a positive result is given and that, with proper technique, this justifies the diagnosis of typhoid fever, a previous attack being excluded. But to a negative result no great importance should be given, as shown by the number of reactions given for the first time late on in the disease. There are a group of results which may be termed "suggestive," in which, while a positive diagnosis is not given, there is some clumping and loss of motility. It is better not to admit such a division to our records, results being put down as "positive" or "negative," but it is impossible not to be somewhat influenced by these partial reactions. Such a finding is an indication to repeat the test in two or three days. The persistence of the agglutinating power of the blood serum long after an attack of typhoid fever may be a cause of difficulty, especially if there be no history of the disease. We are hardly in a position to say to what extent mild attacks of the disease—perhaps not recognized—may be responsible for a reaction being given some time after. In some

persons the persistence of typhoid bacilli in the body may keep up the reaction.

Diagnosis from Other Diseases.—In some instances the diagnosis is entirely in doubt; we know that the patient has fever but are quite uncertain as to the cause. In other cases the patient with typhoid fever is regarded as having some other disease, or vice versa. There are many diseases which may be confounded with typhoid fever.

1. **Tuberculosis.**—The form which gives the greatest difficulty is acute miliary tuberculosis and considering the small number of cases of this disease it is probable that the mistake is relatively often made. Miliary tuberculosis is more often thought to be typhoid fever than the contrary. The difficulty comes from the fact that both diseases may present the same general features without any definite local manifestations. The points which are of special value are as follows: The general appearance of the patient may be of assistance. In tuberculosis there is often a suggestive picture presented by the diffuse cyanosis, which is different from that seen in typhoid fever, associated with an increased respiration rate, although the bronchitis of typhoid fever may be so severe as to increase the respiration rate and cause cyanosis. The temperature curve is often more irregular in tuberculosis and there may be considerable variation in a two-hour chart. The pulmonary signs are usually more marked in tuberculosis; an acute pulmonary emphysema, sometimes local and said to occur especially at the anterior border, is very suggestive of miliary tuberculosis. The pulse may assist, as in tuberculosis it is usually more rapid than in typhoid fever and is rarely dicrotic. A hyperæmic rash, usually of a papular character, or petechiæ especially about the wrists may occur in tuberculosis. These might be mistaken for typhoid roseola. The abdominal condition is of comparatively little aid, for the spleen may be enlarged and diarrhœa or distension occur in both. Hemorrhage from the bowels rarely occurs in tuberculosis. The blood count may be of assistance, as leukocytosis may occur in tuberculosis, but even with a low leukocyte count the increase in the large mononuclears is not found as in typhoid fever. The examination of the eye grounds may show tubercles of the choroid, although this is very rare. A lumbar puncture should always be done in these doubtful cases, as tubercle or typhoid bacilli may be found in the fluid and the diagnosis thus made with certainty. The urine offers little aid as the diazo reaction may be found in both diseases.

In some instances, if bacilli are not obtained, it may be impossible to arrive at any positive opinion. With the progress of the disease a diagnosis may be possible or it may be made only at autopsy. The two diseases may co-exist although this is exceedingly rare.

Tuberculous Peritonitis.—This has not uncommonly been a source of error and the patients are usually thought to have typhoid fever, a mistake more likely to occur if the onset has been comparatively sudden. There is also a variety occurring with more or less continuous fever, abdominal tenderness and some distension, without any palpable tumor, which may give difficulty The absence of sings of typhoid fever and observation for a few days should prevent error, which is probable only if the patient has not been seen from the onset or a correct history cannot be obtained.

2. **Malarial Fever.**—In the majority of cases with careful examination the diagnosis is not difficult. There are certain points to be kept in mind:

(1) There is no such disease as "typhomalaria" or "malarial typhoid." Typhoid fever and malarial fever are associated rarely but there is no third hybrid disease. (2) Any continued fever which resists quinine, properly given in ordinary doses for five days, is not malarial fever. (3) Careful examination of the blood should be made in every doubtful case of continued fever. The type of malarial fever which gives rise to difficulty is the æstivo-autumnal, as in this chills may be absent, remissions of the fever very slight and the general appearance like that of typhoid fever. The intracellular organisms of this variety of malarial fever may be found with difficulty and in doubtful cases the blood should be examined every hour or two, because parasites may be present in the circulating blood only for a short period each day. If crescents are present the diagnosis is easily made. It is doubtful whether puncture of the spleen is justifiable in such cases, for although in the majority without danger, there is some risk. The relation of the temperature curve to the sponging has been of assistance, as in malarial fever the temperature may sometimes be found to rise immediately after the sponge. This is a coincidence in malarial fever but is rare in typhoid fever.

3. **Typhus Fever.**—Fortunately the great majority of the profession have had no opportunity for any practical instruction in the differential diagnosis between this disease and typhoid fever. The probability is that few of us will ever require to make the diagnosis, but it is well to know that the recognition of typhus fever may be exceedingly difficult, especially in a case of sporadic occurrence. Even in localities where the two diseases are prevalent it may be almost impossible early in an attack to make a positive diagnosis. In the case of typhus fever it is evident that this may be a matter of great importance. The onset is of special importance, for in typhus fever this is usually sudden and the temperature rises to 104° or 105° F. within two or three days, which is unusual in typhoid fever. The general features are usually much more severe early in the attack of typhus fever; thus delirium may appear in the first two days and coma be present by the beginning of the second week. Perhaps the most important point to keep in mind is that even in severe attacks of typhus fever the characteristic rash may not be present. The rash of typhus fever usually appears earlier than that of typhoid and the lesions attain their full development within one to three days. In typhus fever the rash is usually uniform over the trunk and extremities, especially over the forearms and legs, while the dorsum of the hands and feet is also frequently involved. It has to be kept in mind that in typhoid fever the rash may be very profuse and petechial in certain localities, while in typhus fever the petechial rash may be very slight. The total duration of the fever in typhus is rarely longer than two weeks and it usually terminates rapidly.

4. **Septicæmia.**—This may cause great difficulty, especially if it be of the cryptogenetic type without any localizing symptoms. There is often a leukocytosis and the differential count shows an increase in the polymorphonuclears. It is in such conditions that blood cultures are of especial value and by them a positive diagnosis may often be made in one or two days. There is one group of these cases to which special reference should be made, namely, those occurring after labor or abortion. Pregnant women who have typhoid fever are subject to abortion or premature delivery and the exact diagnosis may be difficult. The leukocyte count and the result of the blood

cultures are of great assistance. Typhoid fever may appear shortly after delivery and the diagnosis lie between it and puerperal septicæmia. Gonorrhœal septicæmia should be suggested by the local infection, the results of blood cultures and endocarditis, if it be present. Certain cases of pyæmia and pelvic abscess may also give difficulty, especially if they occur without chills or sweats. Irregularity in the temperature curve and early rapidity of the pulse rate are against typhoid fever.

5. **Endocarditis.**—This may frequently cause confusion, especially if it be of the ulcerative type, and offers many points of similarity to septicæmia and pyæmia. The diagnosis may be especially difficult if the patient comes under observation late on in the attack. If he has been seen from the beginning the frequently abrupt onset, the irregular temperature curve and the cardiac condition are all of value. It is well to remember that endocarditis is very rare in typhoid fever and that marked myocarditis rarely appears until well on in the disease. The embolic lesions in endocarditis are often of value in making the diagnosis. Here again the leukocyte count and the results of blood cultures are most important.

6. **Influenza.**—The diagnosis between this disease and typhoid fever may offer difficulty at the onset but rarely later on. We may have much the same general early symptoms and the frequent enlargement of the spleen with influenza is puzzling. Coryza at the beginning of the illness is strongly in favor of influenza and the bronchial symptoms with it are perhaps more likely to occur at an earlier stage. Observation for a few days should prevent influenza being regarded as typhoid fever, but it is not unlikely that many mild attacks of typhoid fever are regarded as influenza.

7. **Febricula.**—This is a very common source of error in the distinction from mild attacks of typhoid fever. In some instances it is only the onset of a relapse that makes the diagnosis between typhoid fever and febricula certain, as the general features may be almost the same. Enlargement of the spleen is quite common in febricula. One point of value may be the fact that with the return of the temperature to normal the patient with febricula often feels practically well. While this may occur in typhoid fever, as a rule even after mild attacks the patient's condition shows much more effect from the illness. The Widal reaction has been of great aid in the distinction of the mild forms of typhoid fever from febricula.

8. **Intoxications.**—There are a number of toxic conditions which we frequently interpret as due to ptomaine poisoning which may give difficulty in diagnosis. The organism often concerned in meat poisoning is nearly related to the paratyphoid group and the general features may be much like those of typhoid fever, with perhaps a special tendency to diarrhœa. In this connection comes the question of the possibility of such attacks being caused by foul gases, sewer air, etc. While this is impossible to prove yet in certain cases there are suggestive facts, as one may see recurring attacks in one house where no explanation can be found in the food supply. As a rule observation for a few days is enough to make the diagnosis clear.

9. **Osteomyelitis.**—In children this has been mistaken for typhoid fever. Leukocytosis and the result of careful examination, especially in the region of the epiphysis, should aid.

10. **The Acute Exanthemata.**—Some of these may give difficulty, especially at the onset and in the absence of an epidemic. Measles, scarlet fever and variola are the most likely to cause confusion. The early erythema

sometimes seen in typhoid fever may suggest measles or scarlet fever. As a rule observation for two or three days will render the diagnosis clear.

11. **Trichinosis.**—Until 1860 this was usually regarded as typhoid fever and is probably sometimes taken for it yet. This disease is probably more common than we suppose and in the great majority of cases is not recognized. In trichinosis the history of eating improperly cooked pork, the pain and tenderness in the muscles, and the œdema, especially of the face, are always suggestive. Rose spots and an enlarged spleen may be present in trichinosis but the spots do not come out in successive crops. The blood examination, showing a leukocytosis with an increased number of eosinophiles, should at once attract attention. The examination of the stools or a piece of muscle will make the diagnosis positive.

12. **Syphilis.**—The secondary stage with fever, marked general symptoms and an enlarged spleen has been mistaken for typhoid fever, but careful examination and observation should make the diagnosis clear.

13. **Miscellaneous Diseases.**—Anthrax and acute glanders without local lesions may occasionally cause difficulty. Relapsing fever in certain localities has been taken for typhoid fever, but the course of this disease and the result of blood examinations should prevent any great difficulty in its recognition. Cerebrospinal fever may cause confusion; the results of lumbar puncture are the greatest aid. Abdominal actinomycosis may simulate typhoid fever.

14. **Malignant Disease.**—In certain instances where this occurs with continued fever, general malaise and no local symptoms or signs, the mistake may easily be made, usually of regarding malignant disease as typhoid fever. It is especially likely to occur where the new growth is situated in the liver and, as noted elsewhere, the two conditions may co-exist and give a very puzzling condition.

In the group just considered the common tendency is to consider another disease to be typhoid fever. There now come a number of conditions in which the difficulty is due to an attack of typhoid fever beginning with marked symptoms in one organ or showing these during the course. Attention being directed to the organ specially involved, the other signs may be overlooked, and a definite although erroneous diagnosis having once been made, it is not easy to see the features which suggest something else. The diagnosis is true so far as it goes but it is not the whole truth.

15. **Conditions of the Nervous System.**—These are frequently a source of difficulty and it is important to remember that meningeal features in typhoid fever may be very marked. A careful search to find tuberculous lesions elsewhere in the body or conditions of the ears and nasopharynx is exceedingly important, but by far the most essential aid in the diagnosis is lumbar puncture, which should be done as a routine in every patient coming in with meningeal symptoms. As a rule this will give the diagnosis at once in the epidemic and purulent and frequently, also in the tuberculous, form of meningitis, while in this last the differential count of the leukocytes in the exudate may be of assistance. In typhoid fever with meningeal symptoms we may find typhoid bacilli in the spinal fluid and so make the diagnosis. It is well to bear in mind that Kernig's sign occurs not infrequently in typhoid fever without any meningeal involvement. It is possible for purulent meningitis to be present during the course of typhoid fever. This may be due to extension from old or new processes in the middle ear, or from

infection from bed-sores or abscesses. There are also rare instances of tuberculous meningitis occurring during convalescence from an attack of typhoid fever.

There are a variety of diseases with nervous manifestations which may cause difficulty in diagnosis, especially such as are associated with fever and more or less stupor. Thus catarrhal jaundice coming on with these features has given difficulty for some days, and also uræmic conditions with fever. It is probable that many of the cases of so-called "brain fever" were typhoid fever with marked cerebral and meningeal features.

16. **Pulmonary Conditions.**—These are exceedingly important, by no means uncommon, and may be especially misleading at the outset. The initial bronchitis may be so severe as to attract the chief attention, but as a rule the increasing, constant fever soon suggests that there is something more. By far the greatest difficulty is found with patients in whom the onset is strongly suggestive of an acute lobar pneumonia. The attack may begin with a chill and the usual physical signs of pneumonia. It may be only after the interval of a week that the persistence of the fever suggests some additional condition and careful examination may then show rose spots. There may be some abdominal pain in these cases, which is likely to be regarded as that which occurs occasionally with pneumonia. It is well to realize that it may be impossible to avoid this error. The patient *has* acute lobar pneumonia and there may be no signs of typhoid fever until the expiration of perhaps a week. In one patient of this series the fever disappeared for a few hours on the eighth day but immediately rose and went through a typical typhoid course. It is well to recognize that this is an error at the outset of the illness which no degree of care may save us from. Goodall, writing of the fever hospitals in Great Britain, states that acute lobar pneumonia heads the list of diseases sent in with an incorrect diagnosis of typhoid fever. The pneumonia coming on in the course of the disease rarely gives rise to much difficulty unless the patient be seen for the first time after it has developed. An atypical form of pneumonia may be present at the onset. This may cause considerable difficulty, particularly if the general symptoms are not severe. In the absence of any of the definite signs of typhoid fever it may be impossible to make a definite diagnosis for some days.

Pleurisy.—The attacks beginning with an acute pleurisy may readily cause error. The diagnosis of pleurisy is correct so far as it goes but there is something behind it. If there be an effusion, routine cultures may make the diagnosis clear but if these be negative it may be difficult to recognize the condition at the onset. The persistence of high fever should cause suspicion.

17. **Abdominal Conditions.**—This is a most important group, as in the first place the ordinary abdominal features of typhoid fever may give difficulty and secondly, the occurrence of abdominal complications before the patient is seen for the first time may be very confusing. Among those of the first group, gastro-enteritis may be suggested on account of severe diarrhœa, but perhaps the most common mistake is to regard the condition as appendicitis. Abdominal pain is comparatively common in typhoid fever, and if it be referred to the right iliac fossa and on examination some tenderness be found, appendicitis is naturally suspected. Muscle spasm is rarely present in these cases of pain in typhoid fever. The leukocyte count is most helpful, for a normal or diminished number of leukocytes speaks strongly against an

acute appendicitis, except in fulminant cases, which are rarely likely to be taken for typhoid fever. The caution may be repeated that under no circumstances should opium be given to a patient with a doubtful abdominal condition. It is well to bear in mind that some of the best surgeons have made the mistake of operating on patients in the early stage of typhoid fever, thinking that there was appendicitis.

The occurrence of abdominal complications before the patient is seen may render the diagnosis very difficult. Thus, in one year, 3 patients of this series were admitted with general peritonitis due to perforation of the intestine. In the absence of rose spots and with a doubtful history it may be almost impossible to make a diagnosis. Fortunately this is not of any great importance as regards treatment, the indications for this being those of the acute abdominal condition. A patient may be admitted with the symptoms of acute cholecystitis, which may even have gone on to perforation. In all such abdominal conditions the presence of the Widal reaction is of great importance in the diagnosis.

18. **Renal Conditions.**—These may cause much difficulty, as the attack may begin with symptoms suggestive of acute nephritis, which may be of the hemorrhagic type. The ordinary febrile albuminuria is not likely to cause confusion.

It may be said of diagnosis that no rules can be set down which apply to all cases. It is well to recognize the fact that diagnosis must often wait for several days' observation. In other instances only an autopsy or some incident during convalescence may make it clear. The more often bacteriological methods are used, the more alert we are to the possibility of mistake, the more care we take in frequent thorough examinations with open minds, the fewer errors will be made.

PROGNOSIS.

"In acute diseases it is not quite safe to prognosticate either death or recovery."—HIPPOCRATES, APHORISM XIX.

There can be no certainty of the outcome or duration of an attack of typhoid fever and it is never safe to give an absolutely favorable prognosis. The patient with every symptom favorable may become seriously ill or have a severe complication without warning, while on the other hand in no disease do we see so many patients recover who have been desperately ill. Many factors have to be taken into consideration, and while those in the patient will be discussed in detail a word should be given to the care which the patient receives. Hard work, stimulated by a spirit which never gives up while there is life, may pull a patient through a desperate attack. This is especially true of those with severe toxæmia, who may owe their recovery directly to the perseverance of the physician and the care of the nurse. In many regards the outlook is better when the patient is treated in a hospital, for there are so many advantages, the better facilities, the constant nursing—possible only in few houses—and the more rapid dealing with emergencies. The method of treatment has some influence and those who use baths are undoubtedly justified in regarding the outlook as more favorable than under any other method of treatment. The stage of the disease at which the patient comes under treatment is an important matter; the earlier he is put

to bed, as a rule the better the prognosis. In patients who have fought the disease and kept about, the prognosis should always be very guardedly given.

There are many factors by which we may estimate the outlook in typhoid fever but it is a disease in which perhaps more than any other we are unable to tell what a day may bring forth. Of the conditions which cause death, we can estimate the danger with some degree of certainty in the most frequent, namely, toxæmia. While it is impossible to say that toxic symptoms may not become more marked later in the attack, yet as a rule the danger of this is slight after the third week, especially under the bath treatment. The response to treatment with hydrotherapy for a few days is a great aid in the prognosis. Sudden death without any warning symptoms may occur during the height of the disease or in convalescence. As regards another factor in the death-rate—the complications—we cannot speak with any certainty, for hemorrhage or perforation may occur without any warning and the outlook be changed in an hour. It is the possibility of these, perhaps more than anything else, which should make us cautious in expressing an opinion. We have large bodies of statistics of the death-rate with various complications but these may be of little help in estimating the chances for a given patient.

There are certain features which may be noted. Epidemics vary remarkably and in some large ones the death-rate has been exceedingly low. Great variation in the mortality may be true of a certain locality from year to year. It may vary in the same clinic and a good example of this is seen in the Royal Victoria Hospital in Montreal, where in the year 1896 among 72 patients there was not a single death, while in 1897 among 75 patients there were 7 deaths. Geographical conditions seem to influence the death-rate very little, for the death-rate from typhoid fever is about the same the world over when large figures are considered.

There may be much difference in the severity of the disease at various periods of the year or at different times in an epidemic. The early cases in the annual typhoid season are often more severe than those coming in after the epidemic begins to diminish. Physicians who have spent many years in the same community often comment on the fact that the virulence of typhoid fever seems to gradually diminish year by year while the disease is endemic and not epidemic. Of the various factors which may influence the death-rate the following may be considered:

Race.—The death-rate in this clinic among the colored patients is just double that among the whites. The diminished resistance of the colored race is an important cause but the lack of care before admission must also be a strong factor.

Sex.—There seems little difference between the two sexes, although in males there is more tendency to keep about after the onset and alcoholism is another factor which renders their death-rate higher. In women the effect of pregnancy has to be remembered, although this must be of slight degree. In the same city the relative mortality in the sexes may vary from year to year, as shown by Curschmann.

Age.—This is of much more importance in regard to prognosis. Up to the age of two years the risk is great; from two to fifteen years is the most favorable period and the mortality is low. As a rule from about fifteen up to twenty-five is a more favorable period than from twenty-five to forty years.

After forty the danger increases with every year and over the age of fifty the death-rate is high.

Occupation and Position in Life.—These influence the mortality principally as they affect the chances of receiving treatment early in the attack. The outlook is better among those who are more likely to be taken in hand early. The group of patients who receive practically no care during the early part of the disease, such as men in lumber camps and construction gangs, tramps, etc., usually have a high mortality. Under like conditions of treatment the occupation has little influence on the prognosis.

General Conditions.—There seems little doubt that newcomers to any locality who contract the disease are apt to have it in a severe form. This is seen in Baltimore among the patients recently come from Europe. As regards constitution, the fat generally give more anxiety than the lean patients, as the infection often seems to be more severe and their resistance less marked. Alcoholics and patients with marked anæmia as a rule have a high death-rate. The co-existence of chronic disease is unfavorable but an exception should be made of cardiac and vascular disease. Patients with arteriosclerosis or well compensated cardiac disease seem to go through an attack of typhoid fever without any marked additional risk. Chronic tuberculosis does not seem to add greatly to the danger.

Special Features.—Toxæmia.—This is an important matter and its degree must always be considered in the prognosis. Delirium, coma and tremors are always of grave omen, especially if they appear early. Of the various types, that characterized by low, muttering delirium associated with tremor is perhaps the most serious. The amount of delirium or stupor, the tremor, subsultus and other disturbances must all be taken into consideration. If the patients are being treated by baths, the effect of these on the symptoms is a great aid and materially assists in giving a prognosis. The estimation of the danger of toxæmia is also influenced by the amount of urine voided, for if the patient is taking large quantities of water and passing urine freely the outlook is more favorable. Where there is difficulty in getting the patient to take water by mouth the prognosis is grave, although the giving of water by the bowel or by subcutaneous infusion may keep up the amount of urine. There are features which may be secondary to the condition of the nervous system or due to the local effect on various organs. Thus meteorism may be an indication of profound toxæmia, just as in pneumonia, but it also has an important effect on account of the local condition in the intestine.

The psychoses occurring early in the attack are of grave significance as regards life but those later in the attack and during convalescence do not materially alter the prognosis. As regards recovery from the mental condition the family and previous history are important. In the psychoses occurring late in the attack, associated with anæmia and exhaustion, the outlook is good.

In the circulation, the condition of the pulse is important and an increased rate is always a grave omen. It may be said that every increase above 120, which is more than temporary, adds greatly to the risk. As has been noted, the death-rate steadily rises with each increase in the pulse rate over 120. The blood pressure is of some assistance in the recognition of a failing circulation and a steadily falling blood pressure with severe toxæmia is a grave sign. The condition of the heart is of importance and especially the

character of the first sound, for if this becomes feeble or inaudible the outlook is always more serious. In others the sounds may become much alike and gallop rhythm or embryocardia be present. Marked cyanosis does not seem to be of any untoward significance.

The various complications in the lung are important. The bronchitis rarely has any influence on the course. The ordinary lobar pneumonia may be the cause of death either early in the attack or later on, when it is probably of even graver significance. Bronchopneumonia is a very dangerous complication, especially in patients who are over forty years of age, and few recover from it. The hypostatic pneumonia is serious more on account of the conditions which have favored its occurrence than for any other reason. Pleurisy, either with or without effusion, adds somewhat to the dangers. The complications about the larynx and epiglottis are serious, especially as they are more apt to occur in patients severely ill, and there is always the danger of œdema of the glottis or bronchopneumonia.

Of the intestinal conditions, meteorism is always serious and should be regarded more as an evidence of the degree of toxæmia than of any local condition. The result of treatment is an important aid in estimating its gravity. Diarrhœa is always a grave symptom, because it usually means either severe toxæmia or a marked grade of ulceration, especially in the colon. Yet, as many of the older writers pointed out, in a patient with severe symptoms, the onset of a sharp attack of diarrhœa may prove beneficial. Hemorrhage is always more or less serious, yet when the figures are carefully examined, it is surprising to find how many of the patients recover. Of the 137 fatal cases in this series only 12 died apparently directly as a result of hemorrhage. Perforation under ordinary circumstances is rarely recovered from, and there does not seem any justification for the view that 5 per cent. of the perforation cases recover without operation. It is more likely that perhaps only one case in several hundreds does so, for the proved cases of recovery from perforation without operation are very few in number. The outlook with operation depends on several factors, perhaps the most important being the time at which it is done after perforation has occurred. There is no question that the sooner operation is done the better the chance for recovery. The extent of the peritonitis and the organism which is present are important, as with a general streptococcus peritonitis the outlook is always extremely grave, while with other organisms it is decidedly more favorable. The condition of the bowel is significant, as in some the whole lower part of the ileum and the cæcum is almost necrotic, so that it may be impossible to make the stitches hold. The general condition and the degree of toxæmia must also be taken into consideration, as a certain number of the patients who have been operated on for perforation die subsequently of toxæmia. Any other complication, such as pneumonia, coming on after the operation, adds greatly to the danger. The death-rate from perforation varies in different years and one hospital may have several successive cases of recovery. It may be that with earlier recognition of the complication we may improve the percentage of recovery.

Among the renal conditions it does not seem reasonable to regard the simple febrile albuminuria as serious. If there be an acute nephritis or the condition of so-called "nephrotyphoid" the prognosis is always more serious. The occurrence of typhoid bacilli in the urine and cystitis are not apparently of any special danger to the patient.

Phlebitis, while distressing, is rarely a cause of death. There are a few instances of detachment of a portion of the thrombus with resulting pulmonary embolism. As regards the outlook for the local circulatory conditions, a very cautious opinion should be expressed, as so many of the patients are left with more or less permanent disability, and it is well to warn them of this at the onset of the thrombosis. The various glandular conditions as a rule are not serious and have little effect on the course but parotitis is an exception. It is always a grave matter and suggests a cautious prognosis. The occurrence of angina with cellulitis of the neck is rarely recovered from.

In considering the prognosis it is important to note the way in which the patient takes his nourishment and especially the amount of water. In general terms the degree of fever is not of great importance. Of course hyperpyrexia is always serious, but most of those who are treating the disease consider that high fever is not necessarily a serious condition. We see this markedly shown in the case of young adults who come in with high fever but no severe toxic symptoms; such as a rule do well and often seem to run a comparatively rapid course to recovery.

Sudden Death.—In the memory of every one who has treated many cases of typhoid fever there must stand out instances of a sudden termination without warning. These impress one so strongly that their frequency has perhaps been overestimated. There were 4 among 137 fatal cases in this series. It appears to be more common in men than in women and the time of its occurrence varies but as a rule it is more common late on in the attack. The most frequent cause is probably myocardial degeneration, with which sudden dilatation or delirium cordis occurs. In certain instances embolism and thrombosis, either of the cerebral or of the pulmonary vessels, may be the explanation. This may follow the detachment of a clot or occur without any evident cause. A profuse intestinal hemorrhage may lead to a sudden termination. In certain patients the association of other diseases may be the cause of sudden death, as in those who have pulmonary tuberculosis and die suddenly as the result of a pulmonary hemorrhage. In some of the cases, however, it may be impossible to give any explanation of the sudden termination.

CHAPTER VI.

THE PROPHYLAXIS AND TREATMENT OF TYPHOID FEVER.

By THOMAS McCRAE, M. D.

"The excreta to which all these fatal prerogatives are assigned are, on their issue from the body, entirely within our power."—Budd.

PROPHYLAXIS.

This is the most important part of the problem of typhoid fever and in the past too little attention has been paid to it, for while we have been willing to give every attention to the patient with the disease we have failed to carry out adequate preventive measures. We talk of infected water and milk as if they were the cause of the disease, forgetting that behind them lies the actual source. Typhoid bacilli do not naturally inhabit water or milk; they may exist in it for a time and even multiply, but their natural dwelling place is man and these are only carriers from one host to the next. The lesson is easy to learn but hard to carry into practice. Let us make sure that every typhoid bacillus is killed immediately on leaving every host and the disease is at an end. If this could be done with every patient in the United States this year, where would the epidemics of next year be? But there are difficulties in the way. Many of the attacks are so mild that the diagnosis is never made and these are unrecognized sources of danger. The country is so infected that it seems almost hopeless to begin the struggle and this applies with greater force to rural than to city communities. Yet every thorough measure of prophylaxis counts, and when we consider how easy it might have been to prevent many epidemics had the proper care been exercised with the first case, there is much to encourage us. We cannot tell how many cases of infection may be prevented by thorough disinfectant measures with one patient. If even the recognized cases are properly handled that reduces the number of the subsequent unrecognized ones. We all need to take the lesson more strongly to heart that with the profession lies the responsibility of seeing to this. And the history of epidemics is often like that of large fires,—a small beginning with increasing extent. An outbreak usually begins with a few cases—a fact well appreciated by Budd—and from these more and more are infected. Take for instance a typhoid fever patient who is living in the area which yields the water-supply of a city. To properly disinfect his excreta involves comparatively little work but let the water-supply of the community be infected from him and what a different condition of affairs there is. Thousands may be exposed to infection and prevention then may involve elements practically impossible to control.

The subject may be considered under three heads: (1) general measures which are for the protection of the community; (2) especial measures in connection with the patient and (3) preventive inoculation.

1. **General Measures.**—These are of wide application and belong rather to the domain of sanitary science. The problem is that of the supply of pure food and water. With the present prevalence of the disease there is practically no community in this country free from a certain degree of danger and the water-supply is everywhere a most important element. All the points relating to it cannot be discussed here, but an important feature is the careful inspection and regulation of the area from which the water is derived. This is more or less uncertain at the best, as it is impossible to inspect a wide area and there may be mild cases of typhoid fever which are not recognized. The next point is the care of the water after it is collected, which means filtration, as it is doubtful if any treatment by chemicals is sufficient. While in cities the obtaining of a pure water-supply is comparatively easy, or should be, it is in rural communities and in country districts that the greatest difficulty comes. Here the prevention of infection from a given patient is all the more important. In fact, as conditions are to-day, it must be the only hope of stamping out the disease, for in a village or on a farm it may be quite impossible to change the water-supply. In all localities where the water is not undoubtedly free of typhoid bacilli, or while the disease occurs, it is important to have the water boiled, but even when this is done there are many sources of danger, for infected water may be used to clean the cooking utensils, to wash vegetables and for personal cleanliness, such as brushing the teeth.

As regards food the difficulties are perhaps even greater, for the sources of supply are so many and food must pass through such various hands that control is almost impossible. Undoubtedly the most likely food to carry infection is milk, which may be infected either accidentally, as in washing the cans and bottles in infected water, or in some instances water may have been added to the milk. In cities some of the distributing points are responsible, as small stores may supply milk to a neighborhood and it may easily be infected in such places. The control of this must be in the hands of the local sanitary authorities. Meats are very rarely the means of carrying infection, except at times the paratyphoid organism, but there can be no doubt that under certain circumstances oysters may do so. This has rarely been the case in the United States, although some instances have certainly been proved, but in England a number of epidemics have been traced to shell-fish. The danger nearly always comes from keeping them in infected water. Vegetables may also be the cause of infection, which in some localities is probably due to typhoid bacilli being blown about with dust, or they may have been washed in infected water. The use of vegetables which have been fertilized by sewage may be a source of danger, especially if they have not been carefully washed.

It is evident that as regards the danger from the above sources the ordinary individual can do little to lessen it. He may see that his drinking water is boiled and that the greatest possible care is taken in the preparation of his food, but he cannot control the matter absolutely. How much more important, therefore, to prevent the necessity by killing the bacilli at the source. During the time of an epidemic every care should be taken to boil both water and milk before using them and all possible sources of infection through either of these should be watched and guarded against. Ice-cream may carry the bacilli past most of the ordinary defences.

The control of the Board of Health should be firm and thorough. Notification ought to be insisted upon and heavy penalties provided for any failure to report all cases with continued fever, whether diagnosed typhoid fever or not. The relation in the health reports of many cities between the number of cases of typhoid fever and the deaths suggests that perhaps only half of the cases are ever reported. The profession are largely to blame for this. One of the greatest difficulties in many communities is the lack of any proper supervision by competent health authorities. The organization of rural hygiene would go a long way toward the solution of the control of typhoid fever. If every state had a staff of men who could be sent to an infected district, carrying laboratory equipment with them, and take control of the situation, we would see a diminished death-rate. Supervision of the method of disinfection could then be carried out most vigorously. There is no reason why this should not be done as carefully as if the patient had plague or cholera.

We are learning in how many instances there is more or less direct contagion. One member of the family brings the disease into the household and others are infected. This might be prevented by more thorough care. In rural communities the one patient may be the source of a small outbreak, and how often the disease is carried into a community from outside is easily realized by a study of the history of epidemics.

We have recently had some excellent object lessons in regard to what can be done in stamping out typhoid fever in small communities. Koch in Germany has shown how important early diagnosis and proper control of the patients can be in controlling the disease. Typhoid fever was very prevalent in Trier. A laboratory was fitted up and by careful methods all the patients —72 in number—suffering from the disease were found. When the diagnosis was made the patient was carefully isolated and thorough disinfection carried out. Within three months no more typhoid bacilli could be found, there were no fresh cases, the patients had recovered, and the disease was stamped out for the time being in that locality. That this was not due to a mere accidental decline of the disease was proved by the fact that in other localities under similar conditions it continued to be prevalent. What has been done once can be done again. It may be objected that we have not the means to repeat this demonstration, but supposing every Board of Health was able to attend to the patients in its district as was done in Trier, it cannot be doubted that typhoid fever would rapidly decrease. We perhaps could not hope for the brilliant results obtained by Koch to be given at once, but every patient properly handled during this year would mean fewer to handle next year.

The German method[1] is to put certain districts under the supervision of a thoroughly equipped institute which coöperates with the local physicians. In all suspected cases examinations are made of the blood, fæces and urine. If typhoid bacilli are found, thorough disinfection and isolation are carried out. Every effort is made to study the source of the infection and precautions taken to limit the spread.

In armies or where large bodies of men are collected together, as in construction or mining camps, special precautions have to be taken. In addition

[1]There is a report on this by Grieg, *Journal of the American Medical Association*, vol. xlvi, 1906; p. 673.

to care in securing a supply of pure food and water there has to be special supervision of the means of disposal of the excreta. In permanent camps this is probably best done by the use of iron troughs which contain milk of lime or crude carbolic acid solution. Overcrowding should be prevented, army camp sites changed frequently, and not used a second time. Every care should be taken to detect the first cases and all men with suspicious symptoms should be isolated at once. Endeavor should be made to keep flies out of the mess tents as much as possible. It has to be remembered that an army on the march usually carries the infection in its own ranks.

2. **Special Measures in Connection with the Patient.**—It is to these especially that we must look if the disease is to be stamped out. This point has been repeated over and over again but until the profession realizes its importance and what is more, carries it into practice, the prevention of typhoid fever is more or less hopeless. Let any man compare his attitude toward a patient with typhoid fever and toward one with plague, cholera or smallpox, and we have the explanation of many of the difficulties. It is the old story of familiarity.

Among the points which have to be considered are the following:

1. **Isolation.**—How thoroughly should we isolate the patient with typhoid fever? In the hospitals of the United States, patients with typhoid fever as a rule are treated in the general medical wards, while in Great Britain they are usually removed to one of the fever hospitals. There is a certain risk in having these patients in the general wards and our duty to attend thoroughly to disinfection is all the greater. But there are advantages in having the patients in a general hospital, for students have an opportunity of studying the disease and certain of the complications, perforation especially, can be handled with more chance of recovery. Yet all hospital records show that there is some danger. When the patient is being treated in a private house it is best to carry out rigid isolation. The room should be prepared as for one of the more infectious diseases, all unnecessary furniture removed, and the other members of the family not allowed in the room. It is well to have separate dishes which do not go down into the general kitchen.

2. **Disinfection.**—Especial attention should be given to the disinfection of the stools, urine, sputum, vomitus and clothing. In addition the bath water should be disinfected and precautions taken against flies. The patient should receive careful attention and after each movement of the bowels the anal and sacral regions should be cleansed with a 1 to 40 solution of carbolic acid or a 1 to 1,000 solution of bichloride of mercury. After micturition, if any urine has been spilled, the same should be done.

(*a*) *Stools.*—The proper disinfection of these is a difficult matter, as the bacilli may be contained in a mass of fæcal material which is penetrated with difficulty. The most effective method is by heat, the fæces with a small quantity of carbolic acid being boiled in cauldrons, but this cannot be done under ordinary conditions, although in military camps it may be the most certain way and was used to some extent in South Africa. This might be used in fever hospitals or during epidemics but in ordinary practice chemical disinfectants must be used, and the most effective of these are milk of lime and carbolic acid. Bichloride of mercury is not a reliable disinfectant for stools. Whichever is used two things must be ensured,—that a sufficient quantity of the solution is used, and allowed to act for a proper length of time. It is well to place a pint of the solution in the bed-pan before it is used and

add an additional amount afterward. The solution and the fæces should be thoroughly mixed and if there are solid masses these should be broken up. The mixture should be allowed to stand for three hours before being thrown out. It is well to keep the disinfecting solution in the bed-pan when it is not in use. Some writers advise the use of a large jar, which can be emptied every day, in which the mixture of fæces and disinfectant is placed and covered by an excess of the solution. (i) Milk of lime. This should be prepared from freshly burnt lime, air-slaked lime being useless, which is mixed with water in the proportion of 100 parts of lime to 60 of water. The lime should be allowed to soak up the water slowly and the resulting hydrate should be kept tightly sealed, as it readily takes up CO_2 and becomes useless. To prepare the milk of lime, one part by weight of the fresh dry hydrate is mixed with eight parts by weight of water; this solution should be prepared every day. It is not safe to depend on the commercial chloride of lime as it may be inert. Care should be taken to see that at least three times the volume of the fæces is added. (ii) Carbolic acid. This should be used in a strength of 1 to 20 and at least twice the volume of fæces added. As a rule the use of carbolic acid is to be preferred, for although the milk of lime is efficient if properly made, to be certain of this requires additional effort and we should use the method which gives the fewest chances for mistake. Disinfection of the stools should be carried on until the patient is convalescent.

(*b*) *Urine.*—The necessity of constant care with this should be impressed on everyone who is handling a patient and especially when the nursing is done by members of the family. The nurses, attendants and orderlies should be taught that the urine of every patient may contain typhoid bacilli and be a source of danger to themselves or to others. The prevention of the occurrence of the bacilli in the urine is an important matter and there seems little doubt of the value of the administration of urotropine by mouth to every patient on two days each week in fifteen grain doses three times a day. Of the disinfectant solutions the two most useful, as shown by Gwyn, are carbolic acid and bichloride of mercury. (i) Carbolic acid. For disinfection in one hour, a third of the volume of urine of a 1 to 20 solution should be used. (ii) Bichloride of mercury. Of this one-fortieth of the volume of urine of a 1 to 1,000 solution is necessary for disinfection in one hour. It is well to add sodium chloride, .5 to 1,000, to the bichloride solution. The easiest method is to place the disinfectant solution in a large covered jar into which the urine is poured; this can be emptied every day. The disinfectant solution should always be in excess and the mixture allowed to stand for at least two hours after the last urine is added before being thrown out. The urinal should be kept in disinfectant solution when not in use.

The urine should be disinfected until the patient is convalescent, unless bacilli are present, when disinfection should be continued for at least three weeks after these have disappeared. No patient should be discharged from observation without the certainty that his urine is free from typhoid bacilli.

(*c*) *Sputum and Vomitus.*—These rarely require disinfection because not often obtained. They should be disinfected by carbolic acid or bichloride exactly as is done with the urine. If the sputum is received in cloths these may be burned.

(*d*) *Clothing.*—The principal danger exists when clothing has been soiled, as necessarily happens very frequently. It is not always possible to detect this, as a few drops of urine on the linen may not be noticed, so that it is safe

to disinfect it as a matter of routine. This is best done by soaking it in a 1 to 20 solution of carbolic acid for two hours and afterward all the linen should be boiled. The rubber sheets may be disinfected by soaking them in 1 to 20 carbolic acid solution. It would probably always be safe to sterilize the mattress by dry heat. Carpets and rugs are better taken up at the beginning of the illness, but if not, there is always the chance that they may have become infected and they should be sterilized by dry heat.

(*e*) *Room.*—Sunlight, fresh air and cleanliness are most important during the illness, but afterward the room should be disinfected by formaline.

(*f*) *Bath Water.*—This must be frequently infected either by small fæcal particles or by urine. Chloride of lime has been found to be the most efficient disinfectant, one-half pound, acting for one hour, being enough for the ordinary tub. This should be used only from fresh tins and not after these have been open for two or three days. The same danger of infection exists in the water used for sponging and for this chloride of lime may be used, or, as the quantity to be disinfected is smaller in amount, bichloride of mercury may be employed.

(*g*) *Bed-pans and Urinals.*—The bed-pans and urinals should be isolated and scalded after each disinfection of their contents. The enema syringes and rectal tubes should be isolated and boiled after using The urinals, syringes and tubes can be kept in one of the disinfectant solutions. The tubs should be cleaned out daily and the canvas strips frequently changed and disinfected.

3. **Flies.**—Every endeavor should be made to keep these away from the patient, as they swarm about and light at once on any fæcal material or urine which is spilled. If possible the windows should be screened but if flies do get into the room every effort should be made to kill them. Netting may be put over the patient but it is difficult to keep this in place with the frequent attention necessary.

4. **Attendants.**—All those who are handling the patient should be especially careful to disinfect their hands whenever the patient has been touched. The hands should be thoroughly washed with hot water and soap and then disinfected in 1 to 1,000 bichloride solution. Nurses should wear rubber aprons when they are giving the baths or sponging the patient. It is important for physicians and medical students to remember that great care should be taken in the examination of the urine, for it is quite likely that infection has resulted through carelessness in this. In a hospital the orderlies should be specially watched, for much of the handling of the patients is done by them and it requires constant care and vigilant oversight to make sure that the orderly who is attending typhoid fever patients carries out all the procedures. It is most important to see that he does not come in contact in any way with the food- or water-supply of the ward and he should not be allowed about the kitchen or permitted to carry any nourishment to the patients. In hospitals it should be the endeavor not to allow the nurse who is handling typhoid fever patients to have anything to do with the food-supply of other patients in the ward. If possible in private practice, the individual who is nursing the patient should have nothing to do with the preparation of the food of the rest of the family. If this be unavoidable the most careful precautions should be taken.

In hospitals and places where the drainage enters into a proper sewage system there is often difficulty in having disinfection thoroughly carried out,

for it is felt that the bacilli are to be carried where there is no chance of their doing further harm. We are not sure of this in any place—oysters may be fattening close to the outlet of the sewer—and besides it is our duty to destroy every bacillus, no matter where it otherwise might go. In hospitals it is most essential for the proper training of the nurses that they carry out the methods very carefully, for if not compelled to do so when in training they are not likely to do it later when among other surroundings.

3. **Anti-typhoid Inoculation.**—The practical application of vaccination as a means of prophylaxis is due largely to the work of A. E. Wright. The material used consists of a bouillon culture of the *B. typhosus* which is grown for four weeks and then sterilized by heating to 60° C. for ten to fifteen minutes. A number of different strains are mixed together and a small amount of carbolic acid or lysol is added to preserve the material. By a special method the virulence of the preparation is measured, and for the first inoculation an amount of the vaccine containing about one thousand millions of bacteria is used and for the second injection about double this number, the two inoculations being given at an interval of two weeks. The amount injected varies from .5 to 1.5 cc. Agar cultures of the bacillus have also been employed, which are less toxic than the bouillon cultures. After the injection there is local redness and pain and frequently enlargement of the neighboring lymph glands. There are generally some constitutional symptoms, slight fever, malaise and perhaps nausea and vomiting, but these usually pass off rapidly without any permanent ill effects. The immediate effect of the vaccination is to diminish the resistance to infection by typhoid bacilli, and if large doses have been given this diminished immunity may be very marked. With this there is a great increase in both the bactericidal and agglutinating elements in the blood. With small doses the increased immunity is less and persists for a shorter time. This has led Wright to advise the giving of two weaker injections in preference to one strong one. It is evident that it would not be wise to vaccinate during an epidemic, as the procedure apparently makes the individual less resistant to infection for a time.

The great majority of the inoculations made thus far have been on the British troops in South Africa and in India. It is difficult as yet to speak positively as to its value but the statistics suggest that it tends both to lessen the liability to infection and also the mortality in those who have been vaccinated and contract the disease. Wright considers that the incidence was diminished about one-half in the inoculated, while the proportion of deaths among them has been rather less than one-half than those among the uninoculated. He quotes the figures as follows: Among 19,069 inoculated soldiers there were only 226 cases of typhoid fever, a proportion of 1 to 84.4, and of these 39 died, which equal 17 per cent. Among 150,231 uninoculated soldiers there were 3,739 cases of typhoid fever, that is, 1 in every 40 took the disease, and the death-rate in this class was 25 per cent. The protection given by vaccination apparently persists for about two years.

It is difficult to predict to what an extent vaccination against typhoid fever may be used in the future. It would certainly seem wise to carry it out among troops who are going to infected districts. In epidemics it should not be used, as already noted. The troublesome symptoms which occur immediately after the injection should not be considered as a *contra-indication.*

Prophylaxis is best attained by killing the bacilli when they leave the patient. Measures to prevent their introduction into healthy individuals are necessary and indispensable but it is like the attempt to kill millions of mosquitoes which might never have been had the eggs been destroyed. Let no one imagine that this is easy to do, for it involves much more labor and conscientious care than the majority of mankind are likely to give. It is in the supervision of this that power given to competent authorities should be so valuable.

TREATMENT.

"It does not follow, of course, that the disease in all cases requires remedies or that a patient should necessarily take medicines because he has the disease."—NATHAN SMITH.

The most important points in treatment are simplicity in the method, care in the nursing, constant watching and common sense throughout. We cannot abort the disease, we have no specific treatment, and the problem is to bring the patient through a severe infection. We should know our limitations and the dangers of misdirected zeal. Among one hundred patients with typhoid fever there is a large proportion who will recover with ordinary careful expectant treatment, a small number who will die despite all care, and an intermediate group the members of which recover or die, depending on our treatment. The decrease in the death-rate comes from saving members of this intermediate group. The most frequent cause of death is toxæmia, a condition which has to be kept in mind in every patient; a smaller number die from complications, and to save some of these the early recognition of the condition is necessary. It has been estimated that probably 8,000 persons in the United States die every year from perforation of the intestine in typhoid fever, and perhaps 2,500 of these can be saved by proper treatment.

It cannot be repeated too often that there is no routine method of treatment. The patient as well as the disease must be considered and the words of Oliver Wendell Holmes may well be kept in mind: "If a doctor has science without common sense he treats a fever but not this man's fever. If he has common sense without science he treats this man's fever without knowing the general laws that govern all fevers." Nor is our duty only to the patient. It is more important to the community that there be no danger of infection to others than that a given patient should be brought safely through an attack. There is just as heavy a responsibility on us to see that the patient's urine and fæces are disinfected thoroughly as to recognize a perforation early enough to give the best chance for recovery. The problem given us is to bring the patient through an acute infection, in which the greatest danger is from toxæmia, and to be prepared to deal properly with the complications. For this latter we must be ready to recognize the condition at once and carry out the proper treatment. To make a prompt diagnosis of perforation is as much our duty as to know how best to treat hemorrhage.

Can we cut short an attack of typhoid fever by any treatment? There seems no proof that we can. Infection having occurred, so far as we know, typhoid fever cannot be aborted any more than scarlet fever or measles. The course of the attack can be modified but more than this we can not do. There are mild attacks of typhoid fever in which the temperature may

be normal within two weeks and the rose spots may appear after defervescence. If a favorite treatment has been used the course is attributed to this, but it is well to remember that such results occur without any drugs being given.

A point which frequently comes up for decision is the advisability of a patient travelling to his home or to a hospital some distance away. The "homing instinct" seems to be very markedly developed in typhoid fever patients and they often insist strongly on taking the journey. If there be no facilities for treatment where they are or if they be seen at a very early stage a short journey may be permissible, but any long travel should be advised against strongly. Patients who have travelled are usually made much worse and the mortality among them is high, while certain statistics have shown that the death-rate increases with the length of the journey.

There is a great difference of opinion as to the giving of a purge at the onset or early in the disease. Many who give no purgatives during the course advocate calomel at the onset, with the idea that the course is modified. The experience of this clinic has been strongly against the use of purgatives at any stage of the disease. It is interesting to note that in many of the patients who have diarrhœa early in the attack, this has followed the taking of purgatives. The less interference there is with the bowels at any stage the less trouble there will be from intestinal disturbances.

The ordinary treatment will be considered under the heads of (1) general considerations, (2) expectant treatment, (3) hydrotherapy, (4) treatment by drugs, (5) eliminative treatment and (6) serum treatment. The general management of the disease will be discussed and then the treatment of special conditions and complications.

1. **General Considerations.**—We have learned slowly that typhoid fever is not a disease to be treated by drugs. Care in the diet, nursing and hydrotherapy are the most important measures. Drugs may be useful for certain conditions but do not enter into the essential treatment. Care and nursing mean much and in no disease do we receive as much aid from an intelligent nurse.

If possible the patient should be treated in a hospital. The advantages of this are many, for in few houses can a patient be handled as satisfactorily as in a hospital. The nursing can be done in a better way, the complications may be recognized and treated earlier and the requisite disinfection carried out more thoroughly. In country practice and in many places hospitals are not available and the best has then to be done in the house. In this event a large, airy room with good ventilation should be chosen. The amount of light should be admitted with which the patient is most comfortable. In summer he may be out of doors for part of the day if the house is so arranged that this is possible. A nurse should be in charge. If this is not possible and the nursing is to be done by the family or by unskilled attendants, careful *written* directions should be given as to the diet, sponging, and disinfection of the stools and urine. These should be specific in every particular and leave as little as possible to the discretion of the attendants. The quantity of nourishment and water to be given ought to be positively stated. Instruction should be given to watch carefully for the appearance of important symptoms, such as abdominal pain, and the conditions for which the physician is to be called at once, ought to be written down. Every detail should be considered, for the sum of minor points may mean much. Indefinite

directions should be avoided. It is well to have a special chart kept so that exact knowledge is possible.

The patient should be put to bed at once, even if the fever is slight or if there is only a suspicion of typhoid fever. We are too apt to temporize and allow a patient with fever but uncertain diagnosis to go about for several days when he should be in bed. This is always a mistake and any fever in a doubtful case should be the sign for complete rest. The woven-wire single bed with a mattress of medium hardness is best. A rubber sheet should be over the mattress, at any rate opposite the centre of the bed, and care should be taken to see that the sheets are smooth. In some cases an air- or water-bed may be advisable. Usually the patient is most comfortable with only one pillow and very light bedclothing. There are certain things to be carried out in every case. Absolute rest should be the rule from the beginning and the patient should not be allowed to get out of bed or do anything for himself which involves exertion. There may be some difficulty in the use of the bed-pan at first but this is usually overcome in a short time. If this should occur, some advise letting the patient sit up, if the attack be mild. This is a matter of opinion, but it is usually possible to accustom the patient to the use of the bed-pan and later it may be essential for him to use it, so that as a rule trouble is saved by insisting on its use from the beginning. More difficulty may be found with urination, many finding great difficulty in voiding while lying flat. Such a patient may be slightly raised or turned on one side, but it is well to be firm and insist on his not getting up, for as a rule this difficulty disappears in a few days. Occasionally retention may require the use of the catheter but this is to be avoided if possible, and hot applications to the hypogastrium or an enema of hot water is often effectual in aiding the emptying of the bladder.

The matter of absolute rest involves the prohibition of visitors, and the fewer people that the patient sees the better. This may be difficult in a private house and can be more easily arranged in a hospital. When patients are very dull, visitors do less harm but in any condition the fewer the better. There should not be any attempt to read to the patient nor should well-meant efforts to amuse him be allowed, for these only tire him to no purpose. Business matters should be strictly forbidden, although distress of mind may be saved by allowing a patient to make arrangements and give directions at the onset of the attack.

There should always be careful attention to the mouth. After each feeding the tongue and teeth should be cleaned and it is advisable to use a mouth wash. The following is a useful formula: carbolic acid (1 to 20 solution), glycerine, āā ℥j (30 cc.), boric acid (saturated solution) ℥viij (250 cc.). The proportions can be changed if desired and it is sometimes well to increase the amount of carbolic acid. Borax and glycerine is also a good combination, while glycerine alone may be freely applied to the tongue, teeth and lips. The nose should be watched and an alkaline spray used if the nostrils become obstructed. In toxic patients, especially if they come under observation late, the mouth may be in a foul condition. Persevering cleanliness and large amounts of water internally are the best aids for this. There is often great difficulty in cleaning the back of the tongue, but the attempt to do this should always be made.

Absolute cleanliness of body is essential. Special attention should be given to the back and it ought to be rubbed with alcohol several times a day.

The dorsal, sacral and anal regions need special care and it is well to have the buttocks washed with a weak solution of carbolic acid (1 to 40) after each stool. A dry dusting powder should be freely used.

The stools should be carefully watched, and it is a good rule for the physician to see a stool at least every two or three days, and every day if there be diarrhœa. The presence of milk curds should be looked for, while every stool containing blood should be saved for inspection. Care must be taken, especially in the country, to prevent flies getting at the urine or stools. Constant attention must be given to the disposal of the excreta and specific instructions should be *written* out in every case, if printed directions are not available. The attendants ought to be warned of the danger of infection and the need of care for their own sake. Certain patients attract flies more than the others, as is often seen in hospital wards where the flies will swarm about one bed. Such patients should be protected by a mosquito net or a covering of cheese cloth.

As to the routine use of alcohol there does not seem any reason why it need be given in an ordinary attack and the great majority of patients will go through the disease without it.

Diet.— The food should be fluid, easy of digestion and absorption. There is a temptation to give too much rather than too little food and more patients are over- than under-fed. Simplicity and efficiency are two important things to be desired in the diet. The main reliance must be placed on milk[1] and there are few patients who cannot take it in some form or other. It is usually better to give it well diluted with water or modified in some way. Four to 6 ounces may be given every four hours diluted with 2 ounces of lime water, an alkaline water, or plain water, or a little bicarbonate of soda may be added to the milk. This gives 24 to 36 ounces of milk *per diem*, which is enough for the majority of patients during the height of the attack. Larger amounts can be well taken by many but are not necessary as a rule. Albumin water is given alternately with the milk. This is made by beating up the whites of one or two eggs with a little water, then straining and adding a little lemon or orange juice and some sugar if desired. To this enough water is added to make 4 or 6 ounces. This makes a palatable drink and is usually given cold. The great majority of patients will go through an attack on the above diet alone, the milk and albumin water being given alternately every two hours. Such a diet is simple, good for the patient and reduces the work of feeding to a minimum; with it digestive disturbances are rare and it can be prepared anywhere, even by unskilled attendants. It combines simplicity, efficiency and cheapness.

Certain modifications may be made. If milk disagrees, if there be abdominal distention, or curds appear in the stools, whey may be substituted for the milk or the egg albumin given alone in larger quantities. Whey is very useful in such conditions; it may be flavored with a little sherry. Buttermilk, koumiss, peptonized or boiled milk may be used or some flavor-

[1] It is important to be sure that the milk is pure. This applies not only to the presence of typhoid bacilli but of other organisms. Many digestive disturbances may be due to the milk, a point to which Edsall has recently drawn attention in reporting an instance in which the milk supply of a hospital was responsible for much intestinal trouble among the typhoid patients. It is always important to examine the milk and its source very carefully, and if there be any doubt the milk should be boiled.

ing, such as vanilla, may be added to the milk. Ice-cream may be given and is especially useful in the feeding of children. Other foods, such as barley water, may be given; bouillon and clear soups may be added for some patients but should not replace the other foods. Cocoa may be tried but frequently disagrees; tea and coffee can be given at any time; iced tea is often very grateful. Beef tea, broths and the various artificially prepared foods are not only not necessary but may be harmful. They are likely to aggravate any tendency to diarrhœa or distension and may well be omitted from the typhoid fever dietary.

If any change from the diet given above be required it is usually in the direction of reduction. Patients do very well on albumin water alone for some time, and there are good practitioners who give nothing but water to their patients during the height of the attack. If there be any digestive disturbance, such as vomiting or diarrhœa, or if undigested curds appear in the stools, it is well to decrease the amount of milk or omit it altogether. There is little danger in a severe attack of the patient receiving too little nourishment.

The question frequently arises as to whether or not the patient should be waked for nourishment. The majority wake occasionally through the night and at these times it is well to give food. Patients with mild symptoms may be allowed to sleep for some hours but as a rule it is well to give nourishment —and especially water—at regular intervals. These may be every three hours during the night, but there is no general rule and this point must be governed by the conditions present. Great care should be taken in feeding patients who are dull and stupid to be sure that they are sufficiently roused and able to swallow before food is given, as otherwise liquids may pass into the larynx and trachea.

Water.—With the question of feeding goes an equally important one—the giving of water. The need of large amounts of water is often forgotten and it is not sufficient to let the patient take water only when he desires it. There should be a constant endeavor to induce him to take larger and larger amounts and while awake he should take water at least every hour. It is a good practice to keep a supply at the bedside so that the patient can help himself if he is able and this may be done easily by a rubber tube. The giving of flavored drinks, such as lemonade, is of help in increasing the amount of water taken. There seems no doubt that we can reduce the severity of an attack by giving large amounts of water, and this is especially important for the delirious and toxic patients, who should be constantly induced to take it. It is well to have a rule that the patient should take 3 liters (100 ounces) of water *per diem* as a minimum and much better 5 or 6 liters. Some patients will take enormous quantities and it is not uncommon for them to void 10 liters of urine in the twenty-four hours, one of this series passing as much as 26 liters. To be certain that a typhoid fever patient is being given enough water requires constant effort on the part of the physician and nurse. If the patient be conscious and intelligent the importance of this can be explained to him and he is usually a willing assistant. Many patients learn that by drinking large amounts of water the fever is lower, they are more comfortable and not likely to have as many tubs. There seems no doubt that the patients who are under this washing-out treatment are likely to have milder attacks. It may be considered a form of internal hydrotherapy.

2. **Expectant Treatment.**—General care as noted above and the meeting of complications as they arise, describe this method. The disease is allowed to run its course with the hope that the outcome may be favorable. No special form of treatment is used, though as a rule some form of hydrotherapy is employed, either sponges or the wet packs.

3. **Hydrotherapy.**—In some form this enters into practically every method of treatment. With patients treated at home the use of sponges or packs may be the only method which can be carried out. Cradles may be placed over the patient to support the bedclothes and, in the air chamber thus formed, ice-bags may be hung or a current of air sent through by an electric fan. This may be combined with wet cloths over the anterior surface of the body, or the patient may be wrapped in a sheet and water frequently sprinkled over it. By such means a considerable amount of evaporation is brought about, but these methods do more for the comfort of the patient than they influence the course of the disease.

Sponges.—These may be given with the water at any temperature but as a rule cold or ice-water is best. Alcohol sponges may be used in some cases. If sponges are given throughout the attack they are usually administered when the patient's temperature is 102.5° or over and as a rule every three hours. It is generally well to use a good deal of water in sponging and the duration should be twenty or thirty minutes. Especial attention should always be given to the back and it is probably well to devote at least half the time to it. With patients who are very feeble and with very young or very old patients, sponges are often the best form of hydrotherapy. They are usually employed for patients with hemorrhage or phlebitis, when lifting into the tub might be harmful.

Packs.—These are useful if there be complications, for children and for delirious patients who cannot conveniently be given the tub baths. It is well to sprinkle the patients with cold water while they are in the pack and the use of fans is helpful, while in severe cases one may combine friction with it. In excitable or delirious patients it is sometimes best to begin with the packs fairly warm and gradually reduce the temperature. It is well to remember that the sponges and packs have no marked influence on the general condition and, while they give comfort to the patient and undoubtedly are helpful, their effect is in no way to be compared to that which follows hydrotherapy in the form of baths, which almost seems to deserve the designation of being a specific treatment. While we are unable to explain this fully, there seems no doubt that the effects of the tub are quite distinct from those which follow the sponges and packs. If begun early in the disease they usually have a marked influence on the course and may be said to be prophylactic as regards many of the dangerous complications. The use of sponges and packs is only symptomatic.

Tub Baths.—With this form of treatment the mortality is lower than with any other, but if used it should be done from the onset and carried out systematically. Brand insisted on the importance of this. It is well to begin the tubs as early as possible even if the symptoms be mild. We can never know how severe an attack may become, and if begun early the bath treatment lessens the likelihood of severe manifestations later in the disease, especially those due to profound toxæmia. To use the baths only in severe attacks or to wait until the patient is desperately ill before beginning them, is fair neither to the method nor to the patient, yet this is not infrequently done.

In discussing the reasons for which the bath treatment is preferred it is evident that the effects on the various systems cannot be strictly limited, for through an improved state of the nervous system all the functions are improved, and this again may be largely due to the increased excretion of toxins.

(*a*) *Nervous System.*—This may be put first, for the nervous symptoms are to some extent an index of the toxæmia. With the baths the severe symptoms usually improve rapidly; delirium lessens, muscular tremors diminish and the mental state clears. If begun early the severe toxic symptoms will not often occur. The old-time severe "typhoid state" is rarely seen in a clinic in which the bath treatment is systematically used.

(*b*) *Increased Excretion of Toxins.*—This occurs largely through the kidneys and is one of the most important results of the baths. The amount of urine and excretion of toxins are both increased, the result of this being seen especially in the state of the nervous system.

(*c*) *Reduction of Temperature.*—Let it be clearly understood that, despite a common opinion, this is *not* the main object of the baths. During the height of the attack the baths may have but little influence on the fever, although markedly improving the general condition; later in the attack there may be drops of one to four degrees.

(*d*) *Circulation.*—There is a great stimulation of the vasomotor system. The heart rate usually falls and the pulse becomes smaller and harder; the soft, flabby pulse before the bath is in marked contrast with the firm pulse after it. There is usually a rise of blood pressure, which is on an average about equal to 15 mm. of Hg. By the condition of the pulse one can often know how long it has been since a tub bath was given. The lymph circulation is probably also affected and through the improved lymph and blood circulation all the systems benefit.

(*e*) *Respiratory Tract.*—With each bath the patient takes at least three or four very full breaths, expanding the lungs thoroughly. This diminishes the chance of passive congestion which is seen very rarely in clinics where this treatment is used. The initial bronchitis is usually greatly benefited by the baths.

(*f*) *Digestive Tract.*—The general absence of gastro-intestinal disturbances is due partly to the baths, but the simple diet and other care are also important. The improved condition of the mouth is marked.

(*g*) *Skin.*—The liability to bed-sores is much diminished, the frequent cleansing of the skin being a good prophylactic. Should boils occur, one tub should be used for that patient alone.

(*h*) *Reduction of Mortality.*—This is the main purpose and follows the improved conditions noted above. By the bath treatment systematically carried out probably five to seven patients are saved in every hundred. There are no more convincing figures than those published by Hare of Brisbane. From 1882 to 1886 in the Brisbane Hospital under the expectant treatment there were 1,828 cases with 271 deaths (14.8 per cent.). From 1887 to 1896 under the bath treatment there were 1,902 cases with 143 deaths (7.5 per cent.). The only change between the two periods was the use of the baths. No figures can be more convincing. Typhoid fever the world over has about the same mortality under the expectant treatment, and while this varies in different epidemics and localities, in any large series will be found to be about 15 per cent. Under the bath treatment a large series will probably show a

saving of five to seven patients per hundred. It has to be remembered that large figures have to be taken and the results of many hospitals combined. The mortality of a given hospital should not be taken alone, for let a hospital gain a reputation for success in handling the disease and it is apt to have patients sent in late in the attack who are in a dangerous condition.

Objections to the Bath Treatment.—There are many urged against it. That it means much work to all concerned is not denied, but is this not a cheap price to pay for saving five to seven patients in every hundred? That they are cruel the writer does not believe, and this is said from observation of many patients and from personal experience. Much depends on the way in which they are given, and every one superintending a clinic should take one himself. No man should carry out the bath treatment without instruction and experience. If many patients make complaint it means that the baths are not properly given. There will always be some complaint under any method, for an attack of typhoid fever is not a pleasant matter at the best, but with care complaints can be reduced to a minimum. The practice of beginning the baths only when the patient is very ill or as a last resort should be condemned. If used they should be begun early and used systematically. That they increase the frequency of complications is not proved, and the incidence of hemorrhage and perforation does not seem to be greater. Relapses may be slightly more frequent but more patients are saved to relapse.

Method of Tubbing.—The baths are given every three or four hours when the temperature is 102.5° F. or over. Even if the fever be persistently high the maximum number of tubs given in the twenty-four hours is 7, for there is usually a little time lost with each tub. The tubs are given for fifteen or twenty minutes. The temperature of the water varies from 70° to 85° F.; there is no routine and the temperature is chosen which does best for that patient. This is an important point to which attention is drawn. As a rule the lowest temperature (not below 70° F.) which the patient stands well should be chosen. The first bath is usually given at 85° and succeeding ones 5 degrees lower until the most suitable point is reached. No ice is used in the tubs, which should be noted as they are often spoken of as "ice baths." Much depends on the first bath, which is best given during the day and with the physician present and as a rule for not longer than ten or fifteen minutes. Should the patient be delirious, the first bath can be given at 70° F. and in these cases cold applications to the head should be used.

A tub on rubber wheels which run without noise is the most suitable. It may be filled outside the ward and wheeled to the bedside, which seems better than having the patient's bed moved to the bathroom. There are various methods in use to support the patient in the tub. In some clinics a stretcher is used, the patient being placed on it and then lifted into the tub. This is useful for very heavy patients. Canvas strips 40 inches in length and with a width varying from 15 to 30 inches are very satisfactory. These are placed across the tub and held in position by clamps on its side which permit of easy alteration in the height of the canvas. The strips are arranged to support the patient at the proper depth and when he is in the tub they can be easily changed so as to make him as comfortable as possible. The head is supported by a rubber ring or pillow. The patient is prepared as follows: The bedclothing and gown are removed under a sheet and if he has been perspiring he should be rubbed dry. It is well to place small pieces of cotton in the ears. The patient is then lifted into the tub by two attendants; one

slips an arm under the patient's head, which is supported in the bend of the elbow, and lifts him by the hands under the shoulders; the other attendant lifts the feet. When they are ready the patient is asked to hold himself stiffly and is then lifted into the tub. This involves only slight exertion and often less than there is in putting the patient on a stretcher. As soon as the patient is in the tub he should be made as comfortable as possible. The canvas strips should be so arranged that the water just covers the chest; with the head properly supported the ears ought to be out of the water. The canvas strips should support the body evenly. A compress wrung out of cold water is put on the forehead and changed occasionally. If nervous symptoms are marked it is well to apply cold affusions to the head frequently. Attention to the little details saves much discomfort and trouble.

While the patient is in the tub he should be rubbed constantly. This is a most important part of the treatment. Brisk superficial rubbing with the flat hand is better than kneading of the muscles. Special attention must be given to the hands and feet, and it is better not to rub the abdomen. During the bath the state of the patient varies greatly; some are comfortable, others shiver and complain of the cold. There may be cyanosis and blueness but these need not cause any alarm. The patients who shiver greatly during the bath and after it, often seem to do very well and it certainly is not a bad sign. The patient should be removed from the tub if there be great distress, unusual cyanosis or collapse, all of which are rare. Vomiting, hemorrhage or complaint of abdominal pain are also indications for immediate removal.

The bed is prepared by putting a rubber sheet over it and on this an ordinary sheet. At the end of the time a fresh sheet is put over the patient in the tub, the wet sheet which has covered him is pulled down to the end of the tub and the patient is lifted out in the same way as he was put in. He is then wrapped in the sheets and covered with one or two blankets. As a rule there is a warm glow and the patient feels very comfortable. At the end of ten minutes he is taken out of the sheets, rubbed dry and the gown and bedclothing replaced. The "after tub" temperature is taken twenty to thirty minutes after the bath. Nourishment or a hot drink may be given during the bath or as soon as the patient is taken out, but alcohol is not required as a routine after the bath. It should be given if the patient's general condition demands it and not because he has had a bath. The patient usually falls asleep after the bath and if conscious generally feels more comfortable. Some may shiver but this is of no moment beyond the discomfort. If there is no reaction, which is rare, hot drinks should be given and hot bottles put around the patient.

It cannot be too strongly emphasized that if there be trouble with the baths there is some fault with the way in which they are being given. The use of water at the temperature best suited for the patient and careful attention to the details which mean so much for his comfort go far in preventing any trouble. There are modifications of the method. The temperature of the water may be kept between 80° and 90° or the gradually cooled bath may be given. Continuous immersion in a bath about body temperature has not proved useful.

The contra-indications to the baths are severe abdominal pain, hemorrhage, any signs of peritonitis or perforation, cholecystitis, phlebitis or great prostration. Warm baths have been suggested for patients with acute nephritis. Patients admitted late in the disease with grave symptoms are not

tubbed as a rule, although if they can take the baths, they are usually benefited. It is well to begin with baths at 85° for a period of ten minutes in such cases, and also with very young or old patients the same may be done or some other form of hydrotherapy used. Menstruation is not necessarily a contra-indication, although it may be well to omit the baths for a day or two. Women patients who are pregnant take the baths perfectly well. Pneumonia and severe bronchitis are not regarded as contra-indications, in fact they are usually improved by the baths.

In private practice one of the portable tubs which can be placed on the bed can be used. This can be filled by a hose and emptied by a siphon, but they are not so satisfactory as the plunge bath.

It may be said again that the tubs should not be used in a routine way for every patient any more than any other form of treatment. Consideration has to be given to the individual and if this treatment be used it ought to be in the way which does best in that particular case. Thus some patients are tubbed only when the temperature reaches 103°, or if there be marked toxic symptoms, even with the temperature below 102.5° the baths are given regularly without reference to the fever. The indication for their use is the condition of the patient, and the temperature is usually a fair guide to this but may not be. In some cases the baths may be omitted during the night.

4. **Treatment by Drugs.**—There is no specific drug treatment for typhoid fever. Many practitioners give a fever mixture, quinine or dilute hydrochloric acid as a routine. If medicine has to be given, hydrochloric acid is probably the best. There are two classes of drugs which should be specially considered.

1. **Antipyretic Drugs.**—These have been given with the intention of reducing or keeping down the temperature, the coal tar products being especially used, but the value of any of them is doubtful. The fever is only a symptom of the infection and to reduce it has no influence on the essential processes of the disease. Then such drugs often do harm by their depressing action. If those of the profession who have used antipyretic drugs in typhoid fever will discontinue them for a time it is unlikely that they will return to their use.

2. **Intestinal Antiseptics.**—These have been used very extensively and many have been employed, such as salol, carbolic acid, chlorine water, β-naphthol, acetozone, etc. That they are of value is not proved. It is impossible to bring about complete disinfection of the bowels, but even if we could, it is doubtful if the disease would be influenced. However, the majority of these drugs do no harm, which is more than can be said of the antipyretics. If the patient is kept on a simple diet, given large amounts of water and the bowels left alone, intestinal disturbance will be at a minimum.

5. **Eliminative Treatment.**—This, as suggested especially by W. B. Thistle of Toronto, is based on the idea that in the toxæmia of typhoid fever we should carry on elimination by the bowel to as great an extent as possible. This may be compared to the elimination which we use in lead poisoning or uræmia. With this in view the bowels are kept freely open throughout the whole course of the disease. Purgation is usually begun with calomel followed by salines and enough is given to produce two or three watery stools a day. With this some intestinal antiseptic, such as salol, is usually given throughout the attack. The patient should take large quantities of water to favor elimination both by the bowel and kidney. It is held that the constant depletion

renders the intestines as free as possible from bacilli, lessens the number in the lymphatic tissues and carries away toxic material. It also constantly sweeps out the bile, while the accumulation of gas in the intestine is prevented and diarrhœa is lessened. A valuable feature in this treatment is the necessity of giving large amounts of water so that the patient is being constantly flushed out. The loose watery stools produced by purgation are in no way to be compared to those due to an irritative diarrhœa. The diet and general management are otherwise the same as in any other method of treatment and hydrotherapy in any form may be combined with it.

6. **Serum Treatment.**—This is as yet in a more or less experimental stage, but we hope that the future will see the production of an effective serum. The work done has been along two lines, bactericidal and antitoxic, but there does not seem any proof of the production of any other than a bactericidal serum. One difficulty, as pointed out by Wassermann, is the lack of sufficient complement in the patient's blood. A so-called antitoxic serum has been used in Paris by Chantemesse. The toxin is obtained in the filtered cultures of typhoid bacilli grown on a medium containing splenic pulp and defibrinated human blood. This is injected into horses and the serum obtained from them. This has been used in a series of 765 patients, 220 of whom were children, with a mortality slightly under 4 per cent., while at the same time in the other Paris hospitals the death-rate varied from 12 to 18 per cent. The earlier the serum was used the more marked was the effect. After its injection the temperature falls and the course may be shortened.

There have been various other serums prepared in much the same way as that of Chantemesse. These may be regarded as being more bactericidal than antitoxic, although for some the latter action has been claimed. In the preparations of these serums—whatever be their value—different strains of the *B. typhosus* should be used. Both on theoretical and practical grounds little is to be expected from the use of bactericidal serums.

The antityphoid extract of Jez is prepared in a different manner. The brain, cord, spleen and bone marrow of immunized rabbits are rubbed in a mortar and an emulsion is made from this. After some time this is filtered and the fluid obtained is held to be antitoxic. It is apparently not bactericidal. Its administration is usually by the mouth in considerable quantities, rarely hypodermically. There are varying reports as to the value of this extract.

Treatment of Special Conditions.—Toxæmia.—When severe this may require special treatment. One of the greatest difficulties is to persuade the patients to take enough water and in this they should be encouraged in every way. If it be impossible to get them to take more than a small amount or if they refuse it altogether, the stomach tube may be passed and 300 cc. of water given through it. This can be done rapidly and the tube passed before the patient realizes what is being done. Salt solution may also be given by the bowel, 250 to 400 cc. every six hours, a soft tube being used and the fluid given slowly. In serious cases, salt solution (750 to 1,000 cc.) can be given by infusion once or twice *per diem*. By these means we can keep up the amount of urine and favor the elimination of toxins. There may also be difficulty in getting these patients to take sufficient nourishment and in this case they may be fed through the stomach tube, milk (150 cc.) well diluted or the whites of three or four eggs in water being given. Rectal feeding may

be used but is to be done with great caution on account of the possibility of ulceration in the rectum.

Alcohol is usually indicated in severe toxæmia and is best given in the form of spirits, either whisky or brandy. Champagne may be used if it agrees better than the other forms of alcohol, but whatever is chosen, care should be taken that a reliable brand is used as adulterated liquor may do the patient more harm than good. The amount of whisky may be from 4 to 12 ounces in the twenty-four hours, but in severe cases even more may be taken. The excretion of alcohol by the breath is a good indication that too much is being given. The best rule for the administration of alcohol is to watch the patient carefully and be guided by the results.

Conditions in the Nervous System.—Headache may be very troublesome and too often is little helped by treatment. The constant application of the ice-bag is often the most useful measure. Small doses of codeia (grain ¼, 0.016 gm.) may lessen it. If the coal tar products are given for headaches, small doses should be used and with caution. If these measures do not relieve the pain and the patient is unable to sleep on account of it, a small dose of morphia may be given hypodermically. This is usually better than giving opium by the mouth.

Delirium is best treated by hydrotherapy, especially the baths, which improve the mental condition, quiet restlessness and are usually effectual without drugs. An ice-bag should be kept constantly on the head of a delirious patient and cold affusions applied while in the tub or being sponged. Special efforts should be made to induce these patients to take large quantities of water and so favor elimination. Great care should be taken to watch a delirious patient constantly and he should never be left alone, for one cannot tell at what moment such a patient may get out of bed, perhaps only to wander aimlessly about the room but in other cases to try to escape through the window. Even when apparently completely prostrated a patient may be capable of great exertion, and it is not safe to relax watchfulness because he seems too feeble to move. The drawsheet is often enough to keep him quiet; it should come up to the chin with the arms underneath. If there be great difficulty in controlling the patient, it is well to use one of the forms of restraining sheets, which is better than struggling with him. A good dose of morphia hypodermically (gr. ¼, 0.016 gm.) is usually advisable. When there is marked restlessness it may be difficult to keep the patient in bed, and for such it is well to have a narrow board along the side of the bed to prevent his falling out. It may be difficult to give the tubs to such a patient and frequent wet packs may be substituted. In hospitals it is well to have small rooms with wire screens on the windows for delirious patients.

Drugs may be of help in such conditions. The bromides with small doses of chloral and codeia may be given but in serious cases it is better to use morphia hypodermically. It is well to remember the importance of sleep for these patients. The patient may thrash around in delirium or lie quietly in coma vigil and for days not be asleep. Probably the best thing we can do for such patients is to give enough morphia hypodermically to secure some hours of sleep. The rare attacks of maniacal delirium are best treated by good doses of morphia hypodermically and the gentlest restraint that is effectual.

Lumbar puncture is advisable for all patients with delirium or profound stupor. It is important for diagnosis but also for treatment. If fluid is

obtained on puncture it may be allowed to run as long as it comes with any pressure, but it is probably well not to withdraw more than 20 cc. at one time. The puncture may be repeated daily if necessary, but the amount of fluid obtained and the relief given are the best guides for its repetition.

The patient with a psychosis in the course of the disease should be kept as quiet as possible, very carefully watched, and hydrotherapy carried on as thoroughly as can be done. It is important that such patients should be well nourished and the diet should be increased as rapidly as seems advisable from the other symptoms.

Alimentary Tract.—Reference has been made to the care of the mouth. If the lips are dry, glycerine may be frequently applied. Especial care should be taken to keep the mouth as clean as possible and to encourage the patient to clear the throat. The complications which occur in the salivary glands are best treated at first by the application of an ice-bag. If there be signs of suppuration an incision should be made, but in parotitis it may be advisable to relieve tension before there are positive signs of pus formation and it is wise to have a surgical opinion early. In the rare cases in which extensive cellulitis of the neck occurs, serious obstructions to the breathing may appear suddenly and the instruments for tracheotomy should be at hand. If there be signs of laryngeal lesions, the mouth should be frequently cleaned, the patient's head kept low, the atmosphere of the room kept moist and preparations made for tracheotomy, which should be done before marked signs of obstruction appear. If there is much difficulty or pain in swallowing, the possibility of ulceration in the œsophagus has to be remembered.

Stomach.—Fortunately there are few gastric symptoms which need special treatment. Nausea and vomiting are rare and if due to disturbance of the stomach itself it is well to cut down the diet to albumin and water or water alone. Small doses of sodium bicarbonate and bismuth subnitrate (āā gr. 10, gm. 0.6) may be given, or the combination of bismuth (gr. 10, gm. 0.6) and cerium oxalate (gr. 5, gm. 0.3) may be tried. Lavage is often helpful if the symptoms be severe. There are some patients who are never able to take more than a given amount of liquid at one time without nausea or regurgitation and this limit has to be carefully observed. Sometimes with meteorism the stomach is enormously distended and the patient is unable to belch up any gas. The stomach tube gives immediate relief and may be passed every few hours as long as the condition lasts. This is especially advisable if the distension is interfering with respiration.

Intestine. Meteorism.—A simple diet with large amounts of water is an important preventive, but constant watch should be kept for meteorism, and treatment begun at once instead of waiting until distension is marked, for a slight amount will often diminish with care in the diet and the giving of a turpentine enema (30 cc. of turpentine to 500 cc. of warm water), and by these means any increase in the distension may be prevented. When distension is marked, the diet should be reduced to albumin or water only. A large flat ice-bag should be applied to the abdomen. Of drugs, turpentine is the most useful and may be applied locally by stupes or given by mouth or in an enema. The turpentine stupes are very useful; they may be applied frequently, but it is wise to alternate them with stupes wrung out of hot water as the constant application of turpentine may cause severe local irritation. The turpentine may be sprinkled on the stupe after it has been wrung out of hot water, but the better way is to mix it with the water (one dram to the

quart, 4 cc. to the liter) and pour this over the cloth, which is then wrung out and applied to the abdomen. The mode of application is simple. A flannel roller is put beneath the patient, a little vaseline is smeared over the abdomen, the stupe is wrung as dry as possible and placed on the abdomen, the edges being rolled under to prevent any dripping, oiled silk is put over the stupe and lastly the flannel binder is brought over all. The skin must be carefully watched lest severe irritation be caused. When given by mouth the usual dose of turpentine is ♏ 15 to 20 (1 cc.) every four hours, but this should not be given continuously for more than forty-eight hours and the urine should be carefully watched, large amounts of water being given at the same time. In patients with nephritis it is wiser not to give turpentine by mouth. When turpentine is given by rectum 1 or 2 ounces (30 to 60 cc.) may be added to a simple enema and care should be taken to see that it is thoroughly mixed with the water. The oil of cinnamon in doses of ♏ 3 to 5 (0.3 cc.) may also be given by mouth and charcoal and β-naphthol are sometimes of help. Eserine has been given hypodermically in doses of grain $\frac{1}{50}$; it probably acts by increasing peristalsis.

The rectal tube may also be used. This should be passed gently for a distance of twelve to fifteen inches, but great care must be taken to avoid any undue force and only a soft tube should be used, as ulcers in the rectum or lower colon have been perforated by a tube. It is usually well to leave the tube in position for about half an hour, turning the patient several times. With some patients, especially if there is a tendency to distention, it is advisable to give a turpentine enema occasionally.

Constipation.—This is to be desired. If the bowels do not move, a simple or oil enema should be given every second day. The possibility of fæcal impaction should be kept in mind and if it occurs the usual treatment should be employed. In this clinic no purgative is given by mouth while there is fever.

Diarrhœa.—This is best avoided by not giving purgatives and by a simple diet. When present it is well to cut off everything except albumin water by mouth and in severe cases give water only. Large doses of bismuth (gr. 30, gm. 2) or acetate of lead (gr. 2, gm. 0.13) may be given by mouth every three hours. The aromatic chalk powder (gr. 30, gm. 2) is sometimes helpful but the astringents seem to be of little use. The question arises as to the advisability of giving opium. Distension is apt to occur with diarrhœa and this is favored by opium; perforation often occurs with diarrhœa and is rarely recognized if opium has been given. In some instances the giving of small doses of codeia by mouth has been useful, but in intractable cases the use of the starch and laudanum enema is most effectual. It will be found possible to deal with diarrhœa without giving opium in the majority of cases. With diarrhœa or incontinence of fæces it is well to keep a large pad below the patient. This may be made of some good absorbent material and should be sprinkled liberally with dusting powder; by its use the soiling of the bed-clothes can be lessened and the danger of bed-sores diminished.

Hemorrhage.—Small hemorrhages and those early in the disease rarely require any special treatment. In the more severe cases the first essential is absolute quiet,[1] generally best secured by a hypodermic dose of morphia, one-

[1] It is a question whether the rule in some clinics not to move the patient for some hours after a hemorrhage, even to change the sheets, is a wise one. There may be danger in severe cases from even turning the patient, but by leaving him on his back for any time bed-sores are almost sure to appear, and is it usually possible to turn him gently without risk.

sixth of a grain usually being enough. The diet should be reduced to albumin water or all food may be discontinued, and it is better to stop stimulants if they are being given. A light ice-bag should be applied to the abdomen. The giving of drugs is of doubtful value. Ergot is probably more harmful than helpful. Adrenalin has been given by the mouth or rectum, while some advise giving small doses in a saline infusion (one dram—4 cc.—of the 1 to 1,000 solution being added to the salt solution). Styptics by mouth are of little value. Some writers advise the giving of turpentine in good doses (℥ 20, 1 cc. every three hours). The most difficult question is as to the advisability of giving opium. Its use is sanctioned by long custom but to what extent bleeding is lessened by its administration is a question not easy to answer. By giving opium we favor distension which in itself is a serious condition. Perforation frequently occurs with hemorrhage, and if opium has been given there is practically no chance of recognizing it before the onset of general peritonitis. As a rule the patients with hemorrhage seem to do better without opium.

The calcium salts may be given as a prophylactic measure, the coagulation time of the blood being taken in every patient, and if it be prolonged, calcium lactate in doses of 10 grains (0.6 gm.) is given three times a day. If hemorrhage has occurred it is always well to give it, for it can certainly do no harm and should be helpful where there is general oozing and perhaps also where the bleeding is from a large vessel. Gelatine injections are of no more value than the calcium salts and are very disturbing to the patient.

Should one use saline infusions after a hemorrhage? In case of very profuse bleeding with the patient exsanguine and in collapse, an infusion should be given, but as a rule the advisability of giving them is doubtful, because in some instances the infusion seems to bring on further bleeding. There need be no alarm about low blood pressure following hemorrhage; this is to be desired as it favors clotting. The use of saline injections as a routine after hemorrhage is not advised.

In some quarters operative treatment has been recommended. This seems of doubtful utility, especially when we remember how difficult it may be to say from which ulcer the blood comes.

It is advantageous to have constipation after hemorrhage and there is no need of moving the bowels for three days at least. For this an oil enema followed by a simple one is usually best.

Perforation.—The treatment of this condition requires no discussion—immediate operation is necessary. But diagnosis must go before treatment, and we should consider it as much a part of our therapeutics to be prepared to make the diagnosis of this complication promptly as to deal with it when it has been recognized. There are some points which may be emphasized.

1. It is the duty of every man who is treating patients with typhoid fever to be as familiar as possible with the symptoms and signs of perforation. There are few men who have the opportunity of studying many cases of it, and if they are seen only at long intervals the impression of the essential features is forgotten from one case to another. For this reason it is all the more important to study as a routine all the abdominal conditions found in typhoid fever.

2. The nursing staff should receive special instructions to report suspicious symptoms at once. These orders are best written out so that there can be no possible doubt. Especial stress should be laid on any sudden abdominal pain

or increase in pain previously present. Nausea or vomiting, a sudden increase in pulse or respiration rate, and any sudden change in temperature, either a rise or fall, are important. When suspicious symptoms appear, the patient should be seen at once. The symptoms immediately after perforation are often so characteristic that the diagnosis can be made more easily then than later on. This is one of the advantages of having the patients in a hospital, especially if there is a senior resident who has had more experience than the junior interne can have.

3. Careful records should be kept in every case. A patient with suspicious symptoms should be watched for some time, the physician staying at the bedside, for the short recurring attacks of pain, so important in the diagnosis, may not last long enough to give time for the physician to be called and see them.

4. Friendly coöperation between the physician and surgeon is important. The surgeon should be given the chance of seeing all patients with suspicious abdominal symptoms, for it is only by such experience that he has a proper chance to judge intelligently of the condition. In a hospital there should not be any delay from red tape; to wait some hours for the visiting physician or surgeon to see the patient may throw away all chance of recovery.

Exploration should be advised in a doubtful condition and can be done under cocaine.[1] No exact rules can be given as to what symptoms and signs justify exploration, but knowledge of the abdominal conditions, constant observation and careful records all help to prevent needless operation. It may be impossible to put into words the reasons which govern one in advising delay or operation. We must remember that our endeavor is to recognize the perforation and not the resulting general peritonitis.

If a perforation is found, the condition present must determine the procedure. A clean-cut opening can be closed by a purse-string suture of fine silk, reinforced by "mattress" satures. Suspicious ulcers may be turned in by the same method. When the opening is closed, the omentum should be brought down over the point of suture. Drainage, for which gauze is best, should always be used if a perforation has been found and is advisable after exploration when no perforation is found, if there be deep ulcers which may perforate later. If there be much distension and general peritonitis, it may be best to bring the piece of bowel with the perforation into the wound and fix it there without any attempt at closure. If the bowel be friable and sutures do not hold, as happens rarely, excision of a part of the bowel and bringing the ends into the wound may be tried, but such cases are almost hopeless. It is wiser not to irrigate but to wipe away the exudate with gauze pads moistened with salt solution. It is important to use gauze drains to the involved areas, and ulcers which seem to be near perforation may be "turned in" by a few sutures.

In all cases the element of haste in operation is important. Close the source of infection, wipe away as much exudate as possible, put in drains and get the patient off the table as quickly as can be done. The possibility of a second perforation or of intestinal obstruction afterward has to be

[1]When it has been decided to open the abdomen it is well to give morphia hypodermically (gr. $\frac{1}{4}$) at once. The abdomen can usually be opened under cocaine and if there be no perforation the incision can be closed with the patient little the worse. If a perforation is found, a general anæsthetic can be given if necessary during the handling of the bowel.

remembered, and if the necessity arises even a desperate condition should not prevent interference, for recovery after three operations is an encouraging fact to remember. Even if the patient be admitted with general peritonitis due to perforation there may still be a chance of recovery, as two of the successful results in this series belonged to this class. In some patients there is no sign of healing in the incision. There is usually severe toxæmia in these instances and the outlook in any case is almost hopeless.

There may be peritonitis without perforation or a simple appendicitis may occur. The symptoms may not differ greatly from those of perforation, and exploration is indicated, the condition found determining the procedure.

Cholecystitis.—In this "border-line" condition the question of treatment is a difficult one. Granted that cholecystitis is present, should the abdomen be opened and the gall bladder drained? The majority of patients with this complication will recover without interference, others will as certainly die. The milder attacks tend to clear up spontaneously and if the patients are carefully watched, delay is usually safe, but there is always the risk of perforation. If the patient be conscious so that a correct idea may be obtained as to pain and tenderness, and if he is in a place where constant watching is possible and immediate operation may be done if perforation occurs, one can wait with some degree of safety. But there is always the risk of waiting too long and after one has lost a patient from so doing, there is more inclination to advise operation in severe cases. For the pain, an ice-bag or hot stupes may be applied but opium should not be given. Tapping the distended gall bladder through the abdominal wall ought not to be done. If the symptoms be acute and the signs pronounced, especially if progressive, operation is the safer course. Opening and draining the gall bladder can be done under cocaine. If perforation has occurred or is strongly suspected, exploration should be done at once. It is not safe to consider that there is no danger of perforation as long as the gall bladder is not palpable, for a much enlarged gall bladder may not be felt or perforation may occur in a non-distended one. If there be doubt as to the condition, exploration is probably safer as it means little added risk, while delay may mean the same, or perforation may occur and the danger to the patient be greatly increased. The exact procedure after opening the abdomen must depend on the condition found but drainage is usually the safer course. It may be advisable to pack gauze about the gall bladder and open it a few hours later.

Abdominal Pain.—This frequently demands treatment. Careful examination should always be made to determine its cause so that treatment may be as rational as possible. Thus if it be due to constipation or a distended bladder, it can easily be relieved or if from distension this can be diminished. The possibility of pain being due to some acute abdominal complication, such as perforation, cholecystitis, etc., must always be kept in mind. If no cause can be found we must use symptomatic measures; thus an ice-bag or turpentine stupes may be applied to the abdomen, while the light application of the Pacquelin cautery is sometimes useful. If the pain is severe and persistent, small doses of bromide (gr. 15, gm. 1) and codeia (gr. $\frac{1}{4}$, gm. 0.016) may be given. If it is very severe and is not relieved by these measures a small dose of morphia (gr. $\frac{1}{6}$, gm. 0.01) may be given hypodermically, but the need for this is infrequent. It is better to give morphia than opium, for severe abdominal pain may be due to an acute abdominal complication and if opium is given the difficulty of recognizing this is greatly increased. By giving

opium for abdominal pain in typhoid fever many patients have gone to a comfortable death without a suspicion even being entertained that a complication, such as perforation, was present.

Respiratory Tract.—Severe epistaxis may be troublesome. The application of cold, the use of astringents, such as alum or adrenalin solution (1 to 1,000) locally, is usually enough to control it, but occasionally it may be necessary to plug the posterior nares with gauze. The initial bronchitis rarely requires any treatment and with the bath treatment it usually clears up rapidly. If it be severe, small doses of a sedative expectorant may be given, but the majority do about as well without any drugs. If there is sputum, this should be disinfected as it may contain typhoid bacilli. Pleurisy should receive the usual treatment and an effusion should be tapped early and an empyema drained immediately. The prevention of the hypostatic type of pneumonia is most important. The bath treatment is a great help in this, but in addition the patient should be kept carefully turned from side to side and supported by pillows so that he lies as little as possible on the back. The importance of this should be frequently impressed on the nurse. When pneumonia is present the treatment does not differ from that usually given and the baths may be kept up with advantage.

Circulatory System.—It is important to keep constant watch not only on the rate and character of the pulse but also on the sounds of the heart. The blood-pressure record is also of value. When the pulse becomes rapid, 120 or over, and the first sound of the heart feeble, it is well to give strychnia, which may be begun by mouth in doses of grain $\frac{1}{60}$ to $\frac{1}{20}$ (gm. 0.001 to 0.003) every four hours. In serious cases it is better to give it hypodermically in the same or even larger doses. The patients stand the drug well and it can safely be given in full doses, even up to grain $\frac{1}{10}$ every four hours for a short time. If there be signs of an overdose, as shown by muscular twitching, etc., all that is necessary is to omit the drug for a few hours. With signs of a failing heart, alcohol is usually a help, and the patient may be given from 4 to 8 ounces in the twenty-four hours. Whether alcohol is to be considered a cardiac stimulant is difficult to say, but the patients seem to use it and be benefited whether it be a stimulant or a food. In patients with a very rapid pulse and marked signs of cardiac failure the giving of digitaline hypodermically, in doses of grain $\frac{1}{30}$ (gm. 0.002) every four hours, is sometimes helpful. As a rule it is better not to give more than four doses in one series but this may tide the patient over a critical period. Saline infusions are sometimes of use, an average amount of 500 to 700 cc. being given. In cases of sudden collapse, camphor (gr. 2, gm. 0.13 dissolved in olive oil) or ether (♏ 20 to 30, cc. 2) may be given hypodermically and repeated doses of the aromatic spirits of ammonia (dram $\frac{1}{2}$, cc. 2) by mouth. As a rule it is better to give drugs such as strychnine and digitaline hypodermically, when this can be done.

Phlebitis.—The leg should be somewhat elevated and kept absolutely at rest on a pillow. The attendants should be instructed not to rub it and to exercise every care when movement is necessary. It may be wrapped in raw cotton and lightly bandaged. The lead and opium lotion may be applied locally. If there be severe pain, general sedatives and even morphia may be required. The patient should be kept quiet for some days after the acute symptoms have disappeared and the leg used very little for at least six weeks. It is well to have the patient wear a bandage for a time and later, if there be

swelling, an elastic stocking should be worn. The treatment of phlebitis in the arm is practically the same as in the leg.

Urinary Tract.—A common difficulty, especially early in the disease, is retention of urine. The necessity of frequent attention should be impressed on the attendants, for very often the patient feels no discomfort and does not ask for the urinal. When the bladder becomes distended it may then be quite impossible for the patient to void. Hot applications over the hypogastrium or an enema of hot water may be effectual, but it may be necessary to use the catheter. Every effort should be made to avoid this, for it means added risk to the patient and additional work to the physician. If it has to be done great care should be taken to avoid infection. The catheterization should be done by the physician whenever possible, as too often in hospitals it is intrusted to the orderlies. If it has been necessary to pass the catheter, it is important to try to have the patient void within three or four hours after being catheterized. One should not wait until he feels the desire to urinate, because sensation is often dulled and the need of emptying the bladder is not felt. The attendants should wait on such a patient at least every three hours. It is well to give large amounts of water, for, as a rule, the more urine that is being voided, the less trouble there is with retention.

The occurrence of typhoid bacilli in the urine must be kept in mind. These have to be looked for, as they may be present without causing any symptoms. It is well to give urotropin (gr. 15, gm. 1) three times a day, on two days in the week, to every patient with typhoid fever. If bacilli are present in the urine, urotropin should be begun at once and may be given in doses of gr. 15 (gm. 1) every four hours by the mouth. The writer has never seen any harm from its use although some cases are reported. If cystitis be present, urotropin should be given by mouth, and it is well to begin bladder irrigations of bichloride of mercury, at first of a strength of 1 to 100,000, gradually increasing to 1 to 50,000. The cystitis may prove very obstinate. The importance of not allowing these patients to go from under observation until the urine is completely clear of organisms may well be emphasized, and it should be part of our routine treatment to be certain that before discharging the patient, his urine is free from bacilli.

The Skin.—Constant care should be taken to keep this clean and special attention should be given to the dependent parts. After each movement of the bowels, the sacral, anal and gluteal regions should be cleaned with a cloth wet with carbolic or bichloride solution. Dusting powder should be freely used. In patients who are very toxic and have incontinence of urine or fæces the care of the skin is a most difficult matter. It is well to use a rubber urinal and keep large pads under the buttocks; these can be easily removed and may save the necessity of changing the bedclothes. When there are signs of redness in the sacral region, it is well to keep the patient on a ring or turn him frequently from side to side, and the rubbing with alcohol and the use of dusting powders should be kept up. One of the best local applications, at the first sign of redness, is a 1 per cent. solution of silver nitrate painted over the area. If any signs of breaking down appear, we should endeavor more than ever to keep the patient off his back, but it is well to remember that when a bed-sore has once begun it may be very difficult to check its course. There are many applications that may be used but perhaps the boric acid poultice, frequently changed, is as good as any. Dusting powders should be used and a constant effort made to keep the area as clean as possible. As a rule dry

applications are preferable to ointments at an early stage, although the latter may be used with advantage when healing begins. If sloughs form they should be cut away at once, and it is well to remember that they may extend some distance under the healthy skin. The usual treatment of bed-sores is the same as that of such ulcers elsewhere. Every effort should be made to keep them as clean as possible, as in some instances they are the source of a general infection.

Boils are troublesome complications, and as one patient may infect another, care should be taken that neither his sponge nor tub is used for other patients. As a rule early incision is the best treatment; this can be done under a local anæsthetic and saves the patient a great deal of misery.

Ductless and Other Glands.—With the first sign of involvement it is well to put on an ice-bag or use hot applications. If there be signs of suppuration it is well to make a free and thorough incision early. Aspiration has been done in some localities, such as the breast, and has given relief, but if there be pus an incision is usually necessary.

Bone Lesions.—Occasionally these come on during the course of the fever. The application of an ice-bag often relieves the pain and periostitis may subside without any other treatment. The areas should be carefully watched and, if suppuration occurs, it is well to incise at the time and leave more thorough surgical treatment until after recovery from the attack. The occurrence of bone lesions in the spine may give considerable trouble. The Pacquelin cautery lightly applied may give relief but sedatives by mouth and even morphia may be required. If the pain be very severe a light plaster jacket should be applied. If coxitis be present, the frequency of dislocation must be remembered and every care taken to prevent this by keeping the leg at rest, either by a long splint or sand-bags, and care should be taken with every movement of the patient.

Tender Toes.—Thorough rubbing of the feet during the baths is an important preventive. When pain is present the application of equal parts of alcohol and tincture of iodine has been found very useful, while in some patients the oil of gaultheria applied locally has given relief. It is always well to put a cradle over the feet to remove the weight of the bedclothes.

Relapse.—The treatment of this differs in no way from that of the original attack. During a recrudescence it is safer to cut down the diet to liquids. The post-typhoid elevations as a rule require no special treatment.

Convalescence.—This may be the most troublesome part of the disease to treat, and the greatest difficulty is in the matter of diet. The writer is conservative in this matter, feeling that while there may be no danger in the early giving of solid food, there is certainly safety in the opposite course. Clear soups, broths, gruel and beef tea may be gradually added to the diet as the temperature becomes normal. In the first few days of normal temperature junket, jellies and soft eggs may be added. Then soft toast may be given about the end of the first week and from the seventh to the tenth day scraped beef or sweetbreads may be given, after this the patient being put on "light diet." By adding a little every day to the dietary the patient is less likely to complain. Reference by the physician to hunger and diet should be avoided and it is often wise to have the additional food come as a surprise to the patient. The smuggling of food by friends has to be guarded against. In all cases the condition of the patient and the character of the attack should be considered. With a coated tongue, a tendency to diarrhœa or after an

attack with marked abdominal features, it is well to be especially cautious in increasing the diet. After a protracted attack or if there be marked emaciation or a psychosis, it may be well to feed more liberally. There is no set rule; the dietary for each patient must be decided by the conditions present.

The patients may be propped up in bed usually from the seventh to the tenth day of normal temperature and allowed up in a chair three or four days later. It is well to have them out in the open air and sunshine as much as possible during convalescence. During this time they should be guarded against excitement and are better not to see many visitors. At first they should see only one a day and the number should be increased gradually. It is generally best not to allow the patients to read too early, certainly not before they are up in a chair. The patients with a persistent slight fever give considerable anxiety; this occurs most often in those who are very emaciated or neurotic. Discontinuing the taking of the temperature or doing so only once or twice a day is often all that is needed. In these patients, if there be no complication, one can increase the diet rapidly even if there be some slight fever. Constipation may be troublesome and for this enemata or olive oil are especially useful. If a purgative by mouth be needed it is well to give castor oil, half an ounce of which may be administered in the evening. The combination of the fluid extract of cascara and glycerine (of each a dram, 4 cc.) given two or three times a day is helpful. Subsequently cascara alone or compound licorice powder may be used. Diarrhœa during convalescence should always be regarded seriously, as it is often associated with ulceration in the colon and may prove very persistent. The diet should be carefully restricted, large doses of bismuth (gr. 30, gm. 2) or zinc oxide (gr. 5, gm. 0.3) given by the mouth and astringent injections used, such as alum, weak silver nitrate solution (1 to 1,000), etc. In very emaciated patients a daily oil rub is useful. Alcohol may be helpful in patients who are exhausted and recover slowly. Iron should be given, if there be anæmia, in the form of Blaud's pills, and there is no objection to beginning its use before the temperature is normal.

There may be marked disturbance of the heart rate, either increase or decrease, especially after any exertion or excitement. These patients should be kept at rest, in bed or in a chair, until the pulse rate returns to normal or near it, and strychnine in good doses should be given. They should increase the amount of exertion very gradually and be cautioned against sudden effort.

An important matter to decide is the length of time that should elapse before patients return to work. With a laborer there is not much difficulty, as he is not likely to return to work until he is physically able, and with an attempt too early, weakness prevents any harm being done. In the case of a professional man the matter is more difficult, and the physician should be firm in insisting on a prolonged vacation. The length of this must depend on the character of the attack, but a minimum of at least three months should be given from the time the patient is convalescent, and in some cases six months will be required. If the patient is very nervous and easily upset by any mental exertion it may be a year before he is able to take up work again. Patients are frequently very much worried by incapacity for mental exertion, and loss of memory, both of which are common after an attack. The physician can safely give a good prognosis in regard to these; time is the best treatment.

Another troublesome occurrence is the falling out of the hair, the likelihood of which is lessened by cutting it short at the beginning of the attack. Should it occur little can be done to check it, except the use of a stimulating hair lotion.

After a severe attack there may be swelling of the legs when the patient goes about, especially in the latter part of the day. It is well to keep these patients quiet until there is no return of the œdema when they go about on their feet. A bandage or elastic stocking may be used.

Sequelæ.—The bone lesions may appear at a long interval after the attack. Their treatment is strictly surgical and thorough excision of the diseased areas is necessary. Œsophageal stricture may be treated by dilatation or, if this prove ineffectual, by operation. The typhoid insanity is probably best handled by an alienist. The matter of the best treatment for these patients may be a difficult one to settle, but if there be a definite psychosis after recovery from the attack of fever it is usually advisable to place them in an institution for the treatment of mental diseases. The post-typhoid neuritis offers no special peculiarities in treatment; massage, electricity and strychnia internally are useful. The typhoid spine is nearly always associated with a general neurotic condition, and for this separation from friends, persistent hydrotherapy and the Pacquelin cautery to the spine are especially useful. A light jacket should be worn for some time and is usually helpful. Cholecystitis as a sequel should be treated by the same methods as during the attack.

It is not uncommon for patients to become very stout during convalescence, but as a rule this condition is not permanent and they commonly lose weight as they regain muscular strength. Persistent enlargement of one leg and the development of varicose veins after phlebitis may be troublesome. The use of elastic stockings may give relief but too often this is a cause of troublesome disability.

The general treatment advised may be summed up as follows:

1. Absolute rest.
2. The diet should be liquid, as simple as possible, and with it large amounts of water.
3. Hydrotherapy, best in the form of the tub baths; if it be impossible to give these, sponges or packs may be substituted.
4. Leaving the bowels alone as far as possible and using enemata if necessary.
5. Drugs to be given only if there be special indications; alcohol not to be given as a routine.
6. Constant vigilance to recognize complications and the knowledge how best to deal with them.

There are certain things which should be done as a routine in the daily examination of the patient with typhoid fever. The general condition, the temperature, pulse and respiration records, the mental state, the condition of the mouth and tongue, the character of the heart sound and pulse, the state of the lungs, especially at the bases, and above all the condition of the abdomen as regards distension, tenderness, pain, extent of the respiratory movements and resistance or rigidity, should all be noted. With this the amount of urine and the number and character of the stools should be observed. It is an advantage if there be a record of the blood pressure and a count of the leukocytes every two or three days. The urine should be

examined frequently and typhoid bacilli looked for. Should symptoms suggestive of a complication appear the records ought to be taken more frequently.

The important points are simplicity in the method, care in the nursing and common sense throughout. We cannot abort the disease and we have no specific treatment as yet. Careful nursing, constant care, and an intelligent knowledge of our limitations and the evils of misdirected zeal, are all essential. The comfort of the patient and the necessity of being sure that he obtains sufficient sleep are important.

In conclusion, "yet is not the sick to be left as desperate because the Disease is not hasty, and kills not suddenly, and out of hand but is drawn out at length, and grants times and occasions to nature of recollecting herself, and to the Physician of giving Remedies."—(Translation, Willis. "De Febribus.")

CHAPTER VII.

TYPHUS FEVER.

By THOMAS McCRAE, M. D.

Definition.—Typhus fever is an acute disease, usually prevailing in epidemics, very infectious and as yet of unknown origin. It is characterized by a sudden onset, a macular eruption, severe toxæmia and a comparatively definite course usually terminating by crisis. The disease has been known by many names, hospital fever, jail fever, camp fever, ship fever, spotted fever, etc. Up to comparatively recent times it was confounded with typhoid fever, malarial fever, relapsing fever, dysentery and the plague. It is perhaps the most infectious of all diseases and therefore occurs as a rule in epidemics, endemic cases being very rare. Typhus fever is much like the acute exanthemata in that it is usually transmitted by direct contact, has a characteristic eruption, runs a self-limited course and is rarely followed by a relapse.

Historical.—The term "typhus" was applied from the time of Hippocrates to a condition characterized by stupor and delirium. In early times the disease which we now designate by this name was confused with others, but from the descriptions of epidemics we can recognize it in many of the older writers. The earliest accounts are of epidemics in the sixteenth century in France, Italy and Hungary. The name "typhus" was apparently first applied to this disease by de Sauvages in 1760. Probably the first to describe the disease was Fracastorius of Verona, who saw epidemics in Italy in 1505 and 1528, in his work "De Contagione et Contagiosis Morbis." He noted its association with famine and war, commented on its contagiousness by the air and described the rash as "lenticulæ, vel puncticulæ aut peticulæ," so that the name petechial fever came into use. In 1542 there was an extensive epidemic to which the name *Morbus hungaricus* was given. In Germany the terms "*Hauptkrankheit*" and "*Hauptweh*" had been given by the people. In England during this century was the first "*Black Assize*" in Oxford in 1577, the name being given because all the court officials contracted the disease from the prisoners brought for trial. The name "*jail fever*" was used as a synonym, and from the prevalence of the disease among camps and armies the names camp or military fever were applied.

In the early part of the seventeenth century there were many epidemics, the disease visiting nearly every country in Europe. In England, Willis described it in 1681 and gave the name "Synochus putrida." During this and the eighteenth century the disease was widely prevalent both in war and peace. The estimates of the numbers who died from it are appalling. In the early part of the eighteenth century the disease was so common that special hospitals were built for it. At this time there were very erroneous views as to its nature and some of the descriptions show that relapsing fever was often confounded. Some writers evidently did recognize the clinical differences from other diseases, especially the plague and relapsing fever and even from typhoid fever, but there was no general acceptation of these views.

During 1812–13 came perhaps the greatest known epidemic, among Napoleon's armies in Russia, but from 1815 to 1846, the disease was rare except in Great Britain and Italy, which caused great difficulty in its distinction from typhoid fever. In France, where there was little or no typhus fever at this time, there was less trouble. In 1846–48 the disease was very prevalent in Great Britain and Ireland. During the Crimean War there was an epidemic at Sebastopol. In 1873 it was in Berlin, 1874–76 in Prag and in 1875 in Vienna. From 1877 to 1882 it was common in Prussia and there was an extensive outbreak during the Turko-Russian War in 1878. There is probably a more or less constant source of infection in Southern Europe.

On the American continent the disease has never been very prevalent. There were epidemics in Canada in 1847, introduced by immigrants, in New York in 1881–82 and 1892–93 and in Philadelphia in 1883. It occurred in Mexico and Cuba in 1906. Fortunately the disease has never had a permanent habitation in this country.

Geographical Distribution.—At the present time typhus fever has disappeared over a considerable part of the earth. It has been a disease rather of temperate and cold climates, Great Britain, Ireland and Russia having especially suffered from it. In the United States there have been no outbreaks for over ten years. Sporadic cases may crop out occasionally at a great distance from any known focus of the disease. There was an example of this in Baltimore in 1901, when three patients were admitted from one house where they lived under very unsanitary conditions and were in contact with foreigners who had recently arrived from southeastern Europe. About the same time a fourth patient was admitted, who had lived in good surroundings, could not possibly have been in contact with the other patients and who had to be regarded as a sporadic case. Fortunately there were no instances of infection from these patients. The disease in epidemics is exceedingly infectious but sporadic cases are apparently not so dangerous, a point on which Murchison laid much emphasis. In epidemics the doctors and nurses are always attacked in large numbers, and there is no disease which has claimed proportionately so many victims from among the members of the profession.

The disease is more or less endemic in Great Britain and Ireland. There are always a certain number of cases each year, but it is well controlled and there is apparently no special danger to the community. In certain parts of Europe, especially the southeast, the disease smoulders, and in certain of the Baltic and Polish provinces, in Hungary and Turkey, it is always more or less present. Southern Italy is also a focus and in northern Africa it is apparently endemic. Persia is rarely free from it but curiously enough in India the disease seems to be very rare. It occurs occasionally in China.

Etiology.—Various organisms have been described but none can be regarded as satisfactorily proved to be causal. We do not know in what way the infection leaves the patient nor how it gains access to the body of healthy individuals, although there are many points which suggest the respiratory tract as the portal of entry. An abundance of fresh air seems to be the most powerful influence in restricting the spread of the disease and the opposite condition of foul air with overcrowding favors its development. The disease does not seem to have a great "striking" distance and the infection does not cross air spaces.

There are varying opinions as to the time of greatest infection, many of the English writers holding that the danger of contagion is slight during the first week, while Curschmann believes that it is greatest at the beginning and height of the febrile stage. There are many instances of infection having occurred in a very short time of exposure, in which it is much like smallpox.

Immunity.—Almost everyone may contract the disease, natural immunity being very unusual. A second attack is very rare, although Murchison had two with an interval of ten years.

Sex and Age.—In widespread epidemics the two sexes are equally attacked, but in districts where the disease exists for some time in partial epidemic form, males are in the majority, as might be expected from their greater exposure to contagion. Pregnancy and lactation do not seem to have any special influence. Fagge states that pregnant women may go through an attack without delivery occurring and if premature delivery occurs the child generally lives if not too immature. Infants are apparently only slightly susceptible but after the age of five years children appear to be almost as much so as adults. The number of adults over fifty years is comparatively large. Among 7,741 cases (Curschmann) there were 12.8 per cent. below 15 years, 65.2 per cent. from 15 to 40, 18.7 per cent. from 40 to 60 and 3.2 per cent. over 60 years of age.

Social Conditions.—These play the most important part in the etiology. Persons living in unsanitary and especially crowded dwellings are very susceptible. With this goes the physical state so greatly influenced by improper or scanty food. Fagge states that of 18,000 patients admitted to the London Fever Hospitals during twenty-three years, 95.7 per cent. had been inmates of hospitals or dependent on parish relief. Privation, starvation and want are powerful influences, while depression caused by fear of the disease, previous exhausting illness or by overexertion is apparently an important element. Patients convalescent from other diseases seem very susceptible and gastro-intestinal disorders render the individual more likely to contract the disease. Alcoholism is an important predisposing factor. The view that tuberculosis confers immunity is probably not correct.

Morbid Anatomy.—The findings after death are not characteristic, except in cases where the typical rash can be made out. The condition is generally such as may be observed after death from an acute infectious disease, and knowing nothing of the history of the subject, it would be very difficult to make a diagnosis of typhus fever from postmortem examination unless the rash was present. The absence of any definite lesions may be the most marked evidence of typhus fever.

Emaciation is usually not present to any extent. Rigor mortis is usually slight and disappears rapidly. Putrefaction occurs rapidly. There are often numerous areas of discoloration over the surface, and if the eruption was present the petechiæ and hemorrhagic areas may be seen. The blood is usually darker and more fluid than normal. Coagulation is apparently diminished and as a rule there are no clots in the heart. The muscles are soft and on section have a deep red color, with hemorrhages into their substance in some cases. Histologically they show marked degeneration, which may be especially marked in the heart muscle.

The Nervous System.—The changes here are comparatively slight. There may be marked hyperæmia of the membranes and occasionally

hemorrhages, which are much more frequent into the membranes than into the brain substance.

The Respiratory Tract.—The respiratory tract shows changes very frequently. The mucous membrane of the pharynx and larynx commonly shows an inflammatory condition with perhaps superficial erosions. In some instances the changes about the pharynx are quite marked and at times perichondritis with necrosis and pus formation is seen. In the trachea and bronchi the mucous membrane is inflamed and at times shows hemorrhages. With the bronchitis there is frequently some bronchopneumonia and collapse, while hypostatic congestion at the bases is common. Lobar pneumonia apparently varies very much in different epidemics; Curschmann notes that in Berlin it was present in 15 per cent. of the fatal cases. Pleurisy may occur but is not very common.

The Circulatory System.—The heart very commonly shows a certain amount of dilatation associated with degenerative changes in the muscles. The arteries do not apparently show much alteration.

The Digestive Tract.—Changes in the mouth are not infrequent and there may be excoriation and fissures in the tongue with ulceration of the gums. The mucous membrane of the stomach and intestine usually shows a catarrhal condition and ecchymoses may occur, but these lesions are comparatively slight. There is no change in the Peyer's patches, although in some cases the follicles in the intestine may show some swelling. The mesenteric glands are not enlarged. Ecchymoses may be found on the peritoneum. The liver may be enlarged, soft and hyperæmic and often shows signs of cloudy swelling. If death occurred late in the disease fatty changes may be present.

The Spleen.—The condition of the spleen depends on the day of disease when death occurred. If this has been during the first week, the spleen is usually found enlarged, but after the middle of the second week this is usually not found. On section the spleen is dark red in color and the pulp is soft.

The Genito-urinary Organs.—The kidneys are usually swollen, hyperæmic and show cloudy swelling. Acute nephritis is a fairly common complication.

Symptoms.—Incubation.—This is usually considered to be between eight and twelve days but limits of four to fourteen days have been observed. The instances given of very short incubation periods are doubtful. As a rule during this period the patients are free from symptoms, although there may be some indefinite discomfort with slight headache and fever.

Onset.—This as a rule is very abrupt with headache, general pains and frequently one or more chills or occasionally chilly sensations only. With the sudden onset there is usually high fever and great prostration, often so marked that it is rare to see a patient who has kept about longer than the second day, while the majority give up on the day of onset. The chill may be repeated and there may be nausea or vomiting. The general appearance at this early stage is often suggestive; the expression is dull and heavy with the face very red and the conjunctivæ showing marked congestion. The tongue is dry and tremulous. The temperature usually rises rapidly and may reach its maximum on the second or third day. With this there may be very severe headache but the patients rarely have much delirium, although they may show the ordinary febrile confusion. In very severe infections or in

alcoholics there may be delirium almost from the onset. The pulse is usually rapid and by the second day may have reached 120, but it is rarely dicrotic. The abdomen shows no special features except that the spleen is generally found to be enlarged very early.

About the third to the fifth day the eruption appears, first on the abdomen, then on the chest and shoulders, then over the back and extremities. The face becomes very much reddened and swollen but rarely shows the characteristic eruption and the palms of the hands and the soles of the feet usually escape also. The rash usually requires from forty-eight to seventy-two hours for its full development. During this period of the disease the patient usually shows very marked mental disturbances and the delirium is often of a violent type. The patient may be quiet or talk and gesticulate when he is excited. At this time he should be watched very carefully as he may jump out of bed and endeavor to escape or attack the attendants. During this period the eruption changes, a certain number of the spots becoming petechial, and with this the eruption becomes much more prominent and has a dirty, bluish color. If with this there be extensive subcutaneous hemorrhages, the skin assumes a curious dusky appearance, which is usually seen about the beginning of the second week. After this the picture changes somewhat, the patient becoming very weak, apathetic and lying in stupor or coma vigil. There may be difficulty in swallowing and incontinence of urine and fæces.

Throughout the attack the temperature continues high, being ordinarily about 104° to 105°. The pulse is usually frequent and toward the end of the attack becomes small and weak. In rare cases the pulse rate is low, which is regarded as a grave sign. Toward the latter part of the second week, if the patient recovers, the fever disappears. This may be anywhere between the tenth and fourteenth day but as a rule is most common from the tenth to the twelfth. Despite the usual description of the termination being by crisis, if the records are carefully examined it will be seen that in the majority the termination is by lysis and occupies about two days. There are, however, certain instances where the termination is by a definite crisis. A defervescence which lasts for four or five days should always suggest some complication.

Toward the end of the disease the enlargement of the spleen disappears and the skin lesions, with the exception of the petechiæ, disappear before the defervescence. The petechial lesions usually show desquamation and remain as brown or yellow spots. With the termination of the fever the skin becomes moist, there may be profuse sweating, the state of the mouth improves and the voice returns to its normal character. Recovery is often very rapid and the patients may have a ravenous appetite immediately after defervescence.

As in all infectious diseases, there are atypical and mild attacks. The older writers described various forms from the predominant symptom. There may be abortive or ambulatory attacks. Death may come in the first week with very severe toxæmia, but as a rule occurs after the tenth day and is usually due to toxæmia. It is rare for death to occur after the second week. Certain special features may be discussed in some detail.

Temperature.—This usually rises very rapidly, may be at 104° on the evening of the first day and reach the maximum on the evening of the second day. The remissions are usually slight and the curve shows little change

until the latter part of the second week, when it begins to drop in the evening. In certain cases there may be a drop at the end of the first week but this is not constant. In the milder cases remissions may occur in the second week and at times precritical drops, analogous to those sometimes seen in pneumonia, are not uncommon.

Defervescence.—This occurs usually from the twelfth to the fifteenth day, rarely being prolonged to the sixteenth or seventeenth. The temperature curve is much like that of the onset and may be with a very sudden drop of perhaps eight degrees in a few hours, but in the majority it occupies a period of about two days. In some cases with a comparatively mild course defervescence has been very protracted, or in mild cases the temperature may show many variations. Defervescence may occur about the end of the first week or be unduly prolonged. In certain of the fatal cases there is a very high temperature before death, while in others there is a fall to below normal, usually associated with a very rapid pulse and great prostration.

The Rash.—The study of this is most important, as on it in many cases the diagnosis must rest and it is practically the only characteristic sign. Many names have been given to it, Murchison quoting nineteen. The eruption may appear from the second to the seventh day but most commonly on the fourth or fifth, and this may vary in different epidemics. An erythematous rash has been described as occurring before the typical one. The eruption consists of two elements,—first, a rash much like that of measles, and second, the characteristic petechial eruption of the disease. The first may appear before the roseola or with it and is especially likely to occur on the chest and abdomen, forearms and legs. It has been termed a mulberry rash and presents a dusky red mottling, which has been described as seeming to be below the surface of the skin. It may disappear before the end of the attack. The specific roseolous rash usually appears first on the abdomen and then about the chest and shoulders. After this it appears on the extremities, while the eruption on the trunk continues to increase in number. The whole rash is usually out within forty-eight hours and a second crop is practically unknown. The face rarely shows the eruption. The number of spots is very variable and apparently bears no relation to the severity of the attack, as in severe cases the rash may be very scanty. As a rule three distinct stages may be observed,—first, a simple hyperæmia; second, a stage when hemorrhage is occurring into the eruption; and third, typical petechiæ. The fresh spot is a pale red macule which disappears entirely on pressure and as a rule is not raised so much as the rose spot of typhoid fever. The color is usually pale, the outlines are more or less irregular, and in dark-skinned individuals they may be very difficult to recognize. It is almost impossible to distinguish them by artificial light. The eruption may not develop beyond this stage but disappear entirely. Should death occur at this time there will be no remains of the rash on the cadaver.

In the next stage the spots become darker, have a dirty reddish color and do not disappear entirely on pressure. This is due to the deposition of blood pigment, which usually begins at the centre and extends to the periphery of each spot. The number of spots which undergo this transformation varies very much in different patients; there may be only a few or they may be so general that they give a curious appearance to the patient. These areas are often most numerous in the inguinal region and over the back. The hemorrhagic change which occurs in the roseola must be distinguished from an

additional petechial eruption, which is exactly comparable to what may occur in other infections. These petechiæ are likely to appear in the latter part of the disease and if abundant are of grave import. They are analogous to the hemorrhagic eruption which may occur in measles. Curschmann states that a slight hemorrhagic eruption occurring in alcoholics is not especially important.

The duration of the hyperæmic eruption is short. If there be no hemorrhagic change, the spots usually disappear by the second or third day, and if the hemorrhagic change is slight the spots persist for from four to six days. When the typical eruption is present the duration is usually from seven to ten days but a certain amount of pigmentation may persist for some time afterward.

There are certain other conditions which are of interest. Among these is a miliary eruption, which may be present late in the attack and is of no special significance. As a rule distinct desquamation is seen after this but it may occur without the presence of sudamina and is comparable to the desquamation not infrequently seen in typhoid fever. Herpes may be present and Curschmann noted them in 5 per cent. during one epidemic. Boils are not common and the period of fever is usually not long enough for bed-sores to appear. In severe attacks, particularly if there has been marked hemorrhage into the skin, there may be areas of necrosis and sloughing. Gangrene has occurred in rare instances. Sweating may occur toward the crisis but is not often profuse. A peculiar odor of the skin, the description of which is much like that in typhoid fever, has been noted by some writers but is not very common. Some of the older writers commented on the special danger of infection when there was a marked odor present.

The Nervous System.—The symptoms due to involvement of the nervous system are important, for there are few patients who have not symptoms of some disturbance. These must be interpreted as due to toxæmia, for organic changes in the nervous system are rare and the fever alone will not account for them, as in some patients they may continue after this has disappeared. Headache is very common, almost constant early in the attack, and with it there may be vertigo and general pains throughout the body and extremities.

The psychical disturbances are very interesting. At the onset the mental condition is usually clear, although the patients may be rather dull and show slow cerebration. Insomnia is common and if the patients fall asleep they are likely to be disturbed by troublesome dreams. As the disease progresses, and usually in the second half of the first week, the mental features become more marked. This may be in one of two ways,—either violent delirium or a condition of marked apathy or almost coma. The delirium is of rather a characteristic type. It is violent and they seem to suffer from hallucinations which are sometimes of the most terrifying kind. The patients are usually very restless and may become violent, requiring to be watched very carefully as there is no knowing at what moment they may become maniacal and do harm to others or to themselves. Thus one patient in this clinic suddenly jumped out of bed, overpowered the orderly and put his fist through a strong wire screen over the window, cutting his arm severely. The appearance of the delirious typhus fever patients is often characteristic and in marked contrast to the delirious typhoid fever patients. They are curiously alert, seem to be watching what is going on around them, frequently try to get out of bed, and with the flushed face and bright eyes present a striking picture. If the hal-

lucinations are of the terrifying kind the patients may be extremely noisy and restless. The onset of severe delirium early in the disease is of bad omen. The other type is that in which coma predominates. The patients are much prostrated, lie quietly in coma vigil, taking no note of their surroundings, and as a rule are in a dangerous state. With this there may be marked tremor, a rapid, feeble pulse, and in some instances the patient is practically in collapse. This condition of coma may be present after the temperature has become normal.

Tremor is one of the common severe manifestations and may be only slight or so general and severe that it suggests a convulsion. Subsultus tendinum with picking at the bedclothes is common. Actual convulsions have been noted. Naturally these severe nervous manifestations are associated with a grave prognosis. In some cases there have been tonic contractures and at times muscular cramp may be very distressing. Sensory disturbances are sometimes troublesome at the onset and may also occur in convalescence, the descriptions of some writers suggesting a condition resembling the "tender toes" of typhoid fever. Organic changes in the nervous system are not common, although meningitis has been reported. Hemiplegia has occurred but is rare and is due to meningeal hemorrhage or to embolism or thrombosis. Neuritis may occur but is evidently not common.

Special Senses.—The characteristic appearance of the eyes due to the injection of the conjunctivæ has been noted. Hemorrhages into the conjunctivæ may occur in severe attacks and in some patients with marked coma vigil there may be ulceration. Disturbances in hearing, especially deafness, are not uncommon and apparently largely due to hyperæmia; otitis media may occur.

The Respiratory Organs.—Epistaxis has been noted early in the disease. A catarrhal condition of the nose and pharynx is very common at the onset, frequently extends down the trachea and bronchi, and sets up an irritative cough with which there may be very little expectoration. Accompanying this there is often some change in the voice, the hoarseness being associated with the catarrhal condition. While this may clear up entirely, yet in a certain number of cases more serious changes may occur, such as erosions and fissures, which gradually develop into extensive ulceration. Following this, ulceration of the cartilages often occurs and in some instances there may be serious œdema. These conditions are always of grave import, both on account of the local condition and the danger of pulmonary infection, while, should the patient recover, permanent changes in the larynx are common. In the lungs there may be bronchopneumonia, hypostatic congestion or lobar pneumonia, all of which are serious. Pleurisy occurs not infrequently and if with pneumonia, empyema may follow.

The Circulatory System.—The changes here show no special peculiarity. With the severe toxæmia there may be myocarditis and some dilatation. The pulse early in the disease is usually rapid, small and of low tension. Dicrotism is rare. In the second week the pulse becomes small and at times irregular. A slow pulse rate is occasionally seen. The heart sounds show considerable change, the first becoming much like the second and later in the attack disappearing entirely.

The red cells are said to be usually increased in number. Leukocytosis generally occurs. Love reports the average for 26 cases as 24,000, with an increase specially in the polymorphonuclear cells. He noted that in the

blood of the fatal cases no eosinophiles were present but they were never completely absent in the blood of the non-fatal ones and considers that the absence of eosinophiles does not necessarily mean that death follows but does mean a grave prognosis. In the non-fatal cases there was usually a slight increase in the large mononuclear elements. There was usually an increase in the leukocytes after the appearance of the eruption. In the four cases in the Johns Hopkins Hospital there was leukocytosis in all, the average of the highest counts being 22,000. The highest count of 32,000 was shortly before death in a patient who at death had a normal temperature. After the attack there may be a slight anæmia.

The Digestive Tract.—The tongue is usually furred, and as the disease progresses, it and the lips are likely to become fissured and covered with sordes. In severe attacks it is almost impossible to avoid dryness of the mouth and deposits of mucus and crusts may be found over the soft palate and tonsils. Gastric disturbances do not often occur. The bowels are usually constipated, although there may be diarrhœa. If the rash be of marked hemorrhagic type it is quite possible that there may be hemorrhage into the intestine which may give some bleeding from the bowel, but such cases are rare. Jaundice has been noted during the second week, probably toxic and analogous to that seen in many other infections. There is usually bile in the stools.

The Genito-Urinary Organs.—Changes in the kidney are such as may occur in any acute febrile disease and albuminuria is common, usually appearing about the third or fourth day and lasting until defervescence. In rare cases there may be a definite nephritis, which is always serious. The diazo reaction is obtained in a considerable number of cases. Retention of urine is said to be uncommon in males but quite common in females. Orchitis is very rare. Menstruation is usually suspended during the attack, although occasionally it may occur with the onset. Pregnancy does not afford any protection against the disease, but the danger of abortion is probably less than in any other severe acute disease and it is less likely to occur during the later months of pregnancy. In some instances when pregnancy has been interrupted there has been considerable danger from uterine hemorrhage.

Variations in the Disease.—There may be great variation from the usual course, as is true of all the acute infections. Thus mild attacks occur and the patient goes through the disease without any serious features. In others the attack may be both mild and short so that their recognition offers great difficulty. Curschmann describes a certain group of abortive cases which begin with severe symptoms, the temperature being high at first and then falling rapidly. Somewhat like these is a group of cases seen especially in physicians and nurses who are handling patients with the disease, in whom there are symptoms suggestive of a slight toxæmia. They usually recover quickly as soon as they are removed from contact with the patients. Ambulatory cases are said to occur, but when one remembers the usual severity of the attack these must be rare as compared with typhoid fever. Malignant attacks are seen, especially in epidemics, with death on the second or third day. Hemorrhagic cases occur as in the other acute infections.

Sex does not appear to make any special difference except that males are more likely to have a severe infection and furnish a larger proportion of

alcoholics. Typhus fever in childhood is not very common and the course of the disease is usually milder; the majority terminate between the eighth and the twelfth day, and the death-rate is much lower than in adults. Convulsions are not uncommon at the onset and the nervous symptoms are apt to be especially marked. In advanced life the disease is serious, especially in patients over fifty, the danger being from cardiac weakness and the tendency to pulmonary complications.

Relapse.—This is exceedingly rare and for ordinary purposes the probability of its occurrence may be disregarded. Among 18,268 cases in the London Fever Hospitals there was only 1 case of relapse. It has been pointed out that a genuine attack may follow an abortive one.

Association with Other Diseases.—There are rare instances in which typhus fever co-exists with one of the acute exanthemata, but some of these may be instances of the rapid succession of one infection after the other. A point of interest is the possibility of typhoid and typhus fevers occurring together. There are some instances of a patient with typhoid fever being sent by mistake into a typhus ward and contracting the disease. Diphtheria may co-exist, but in the absence of definite bacteriological findings the diagnosis is doubtful, owing to the frequent occurrence of membrane over the pharynx in typhus fever. Relapsing fever and typhus fever have been noted as co-existing. Tuberculosis, especially the acute miliary form, may be present with typhus fever and it is possible that the latter hastens the development of the tuberculosis. Patients with chronic tuberculosis may contract typhus fever just as any one else. Curschmann considers that chronic alcoholics are prone to contract the disease and that the course is usually more severe, as they are especially apt to show severe nervous manifestations, while cardiac failure and renal changes are common. As might be expected debilitated persons stand an attack badly, and fat persons are usually bad subjects.

Convalescence.—This is usually rapid and the patients are often hungry soon after the temperature becomes normal. As a rule the nervous symptoms disappear with defervescence, although delirium or mental confusion may persist for a few days. Some apparently continue to be troubled by the hallucinations of the delirium. True psychoses are rare. Hemiplegia and paralysis do not often occur. Subnormal temperature is very commonly present during the first week of convalescence and the pulse may continue rapid; bradycardia sometimes occurs. Neuralgia is said to be fairly common. Following laryngeal ulceration, infection of the lungs may occur, or there may be permanent local damage.

Prognosis.—In slight epidemics the death-rate may not be higher than 10 or 15 per cent., while under unhygienic conditions it may rise to 20, 30 or even 50 per cent. In hospitals during epidemics the average mortality is from 20 to 25 per cent. Murchison's series of 18,592 showed a mortality of 18.78 per cent The effect of age is marked; thus in children below the age of five years the death-rate is high but from ten to fifteen years is low, while over the age of fifty it is high. The position in life influences the mortality, for those who have been living under poor conditions of sanitation or in crowded surroundings are more likely to die. Alcoholism is a serious feature in the prognosis. The influence of overexertion is of interest, for in epidemics a large proportion of the physicians, nurses and attendants who take the disease die of it. The individual exhausted by hard work probably has less

resistance. The conditions under which the patients are treated influence the mortality. The death-rate is lower if they can be removed from unsanitary surroundings to a good hospital. The amount of air-space given to each patient materially affects the outlook.

As in all infections there are certain groups of cases which differ from the average in prognosis. Thus the form of severe infection spoken of as *typhus siderans* is almost always fatal, death occurring by the third or fourth day and perhaps even before the rash is completely out. The hemorrhagic form usually ends fatally, although if the hemorrhagic process makes its appearance late, the prognosis is more favorable the later it appears. With hyperpyrexia the prognosis is usually grave, although a high temperature early in the attack is not of especially bad omen but its persistence is serious. The condition of the circulation is important; the pulse is rapid early in the disease as a rule, but if with this it be soft and easily compressible or irregular, the outlook is grave. The appearance of pulmonary complications is serious, especially in the older patients and with extensive bronchitis there is always the danger of bronchopneumonia. In the digestive tract one of the most serious conditions is meteorism. A diminished amount of urine or the presence of very large amounts of albumin and especially the onset of an acute nephritis are of serious import. The early onset of severe nervous manifestations is a grave matter, while coma vigil with much muscular tremor means severe intoxication. Many writers have stated that marked contraction of the pupils is a serious sign. As regards the character of the rash, leaving out the cases which are of the hemorrhagic type, there is little to be said. Gangrene is always a very serious condition. Curschmann lays emphasis on diffuse cyanosis of the face and hands as being a grave sign.

Diagnosis.—In an epidemic this is likely to offer comparatively little difficulty, but when cases arise sporadically, it is well to remember that immediate recognition may be very difficult, as is likely to be true of any acute infection which the profession has had little opportunity of seeing. We know the difficulty which is often found in recognizing smallpox at the onset, particularly in a somewhat atypical case, by those who are unfamiliar with it. That there may be difficulty even during an epidemic was well shown in New York in 1881, when a large number of patients with other diseases were sent to the Typhus Fever Hospital. A recent instance occurred in London where three patients with typhus fever were sent to a fever hospital with the diagnosis of typhoid fever. The mistake of considering other disease to be typhus fever is most likely to be made during epidemics; with sporadic cases or the early ones of an epidemic we are more likely to make the opposite error and mistake typhus fever for some other disease.

Diagnosis at Onset.—The onset may offer points of resemblance to several of the acute exanthemata, especially smallpox, scarlet fever and measles. Relapsing fever, meningitis and septicæmia may also give difficulty. In the acute exanthemata we may have the same sudden onset with a rapidly rising fever, severe headache and marked prostration, and until the eruption appears it may be impossible to make the diagnosis. In the recognition of smallpox, the occasional, early scarlatiniform rash is important, while the characteristic rash of smallpox usually occurs on the face early in the attack, while in typhus fever the face is usually but little involved. The drop in temperature with the appearance of the rash in smallpox may be of assistance. There may be special difficulty in the differentiation of the hemor-

rhagic form of typhus fever from the similar form of smallpox, as either may end fatally before the characteristic rash is fully developed. There may be the same difficulty in distinguishing the disease from scarlet fever or measles. The characteristic appearance of the tongue, on which so much stress is laid by McCollom, may be of help as regards the former, while the early coryza, bronchitis and Koplik's spots would assist in the recognition of measles. In all these cases the history and the possibility of exposure to any infection must be considered, but the greatest difficulty arises when no help is obtained from these. In any such doubtful case the physician must recognize that care should be exercised before a positive diagnosis is made and that in certain instances it is necessary to wait. No man may be able to make a diagnosis until after some period of observation. It is evident that during this time the patient should be rigidly isolated.

Relapsing fever may cause difficulty, especially as the diseases arise under the same conditions, but examination of the blood and the subsequent course should make the diagnosis clear in a very short time. The co-existence of the diseases has to be kept in mind. Cerebrospinal meningitis may suggest typhus fever, especially if there be a rash with it, but the result of lumbar puncture will usually render its diagnosis clear. Septicæmia, and especially the type with a latent endocarditis, may give great difficulty. The result of blood cultures may be positive but in some cases it will probably be necessary to observe the patients for several days before a positive diagnosis can be made. Plague may give difficulty and also perhaps pneumonia at an early stage. Influenza may show features much like typhus fever but the absence of leukocytosis should be of help. Malarial fever, certain forms of purpura and typhoid fever with a sudden onset may all give difficulty but careful examinations and continued observation should soon give the diagnosis. Uræmia, probably with a severe terminal infection, has also been confused with this disease. It seems reasonable to conclude that with a sporadic case of typhus fever the diagnosis before the appearance of the rash will be most difficult and can rarely be made with any certainty.

Diagnosis in the Stage of Eruption.—In typical cases this is not likely to offer much difficulty, which is true of disease generally, as it is the atypical cases that give the difficulty and for them no definite rules can be given. The diseases which have to be especially considered are typhoid fever, measles, purpura and some of the other acute infections. It must be kept in mind that the rash of typhus fever may show great variation from the usual descriptions and it is such cases that offer the greatest difficulty in diagnosis from typhoid fever. The onset of typhoid fever is usually more gradual, the early symptoms very much less severe, and it is rare to have severe nervous manifestations early in the course. The pulse in typhus fever is much more rapid early in the disease and is rarely dicrotic. The enlargement of the spleen is common to the two diseases but appears early and disappears early in typhus fever. As a rule there is leukocytosis in typhoid fever and the result of blood cultures or the Widal test may make the diagnosis positive, but the diazo reaction is not of assistance. The eruption in typhus fever is usually at first only hyperæmic and not hemorrhagic and the number of areas that become hemorrhagic may be few, while on the other hand a certain number of the rose spots in typhoid fever may become hemorrhagic. There are certain distinctions in the character of the individual spots, for those of typhus fever are rather indistinct hyperæmic patches which gradually

become darker and are not papular, while the spots in typhoid fever are more elevated, have moderately sharp outlines and are papular. The rash of typhus fever appears much earlier than that of typhoid fever and continues to appear in definite succession so that the ultimate number is reached within a few days, while in typhoid fever the rash appears in successive crops. Then in typhus fever the eruption is fairly even over the body and extremities and usually common on the hands and feet. In typhoid fever the eruption is rarely present on the extremities and the hands and feet escape. The general appearance of the patient is often suggestive. The curious wild look with swollen, red face and injected eyes (sometimes termed the "ferret eyes") of the typhus patient is in contrast to the ordinary dull, stupid appearance of the one with typhoid fever.

The rash of measles, especially early in the attack, may be much like that of typhus fever, and if in the latter disease the measles-like eruption, sometimes present, is marked, there may be great difficulty in the diagnosis. The face is generally attacked first in measles, while as a rule it escapes in typhus fever. The appearance of petechiæ should make the diagnosis clear. Careful examination should always be made for Koplik's spots. In measles with the appearance of the eruption there is usually a drop in the temperature, which does not occur in typhus fever.

Purpura is not likely to give difficulty for any length of time. The occurrence of insect bites in patients who are suffering from fever may cause difficulty, but careful examination of the lesions will probably show the mark of the bite in the centre. A copaiba rash has been mistaken for that of typhus fever. Anthrax and glanders have given difficulty in rare instances.

It may not be possible to make a positive diagnosis when the patient is first seen. Although the disease is rare, yet its possibility should be kept in mind when a patient is seen in an illness with an abrupt febrile onset and features which give difficulty in diagnosis.

Treatment.—We have two duties, one to the patient and the other to the community. In handling a disease so infectious as this, every precaution should be taken to prevent or lessen the chance of infection. The usual rules regarding isolation should be most rigidly carried out and wherever possible the patients should be removed to special hospitals. In case of an epidemic in this country it would probably be best to treat the patients in temporary barracks or if possible in tents which should be erected in open spaces and away from dwellings. It has been found important in epidemics to carry out periodical careful inspection of the most crowded districts and unsanitary localities in the community, for by this cases may be recognized early, and isolated. Two points seem to be especially important in limiting the spread of infection,—large air-space and thorough ventilation. Physicians and nurses should not be allowed to work too many hours in succession and should spend as much time as possible in the open air.

The most careful precautions should be carried out. The room from which the patient has been removed should be thoroughly disinfected and the bedding, carpets, etc., either sterilized by steam or burned. Clothing should be at once placed in 5 per cent. solution of carbolic acid and subsequently boiled. For the other articles ordinary rules should be applied. In the present ignorance regarding the mode of infection it is well to carry out careful disinfection of the urine and fæces, which may be done in the same way as for typhoid fever. After the attack, the rooms occupied by the patient

should be disinfected and well aired for several days. The patient should be given warm baths for some days before discharge and be sponged with some antiseptic solution, especial attention being given to the head. The bodies of those dead of typhus fever do not seem especially dangerous but should be wrapped in a sheet wrung out of a 5 per cent. solution of carbolic acid. There does not seem to be any great danger of infection in handling the bodies or doing autopsies.

We have no specific treatment for the disease. We have to deal with a severe toxæmia and with certain complications, especially of the respiratory tract and circulatory system, which are to a considerable degree secondary to the toxæmia. Consequently our endeavor must be to keep the patient in the best possible condition, nourish him as well as we are able and favor the elimination of toxins. The patients should be put to bed at once and kept absolutely at rest. The diet should be fluid; milk and its modifications, albumin water, broths and eggs may all be given. It is probably well to feed at frequent, regular intervals and care should always be taken with those who are dull and stupid that food does not pass down into the respiratory tract. Large amounts of water should be given and the endeavor made to increase the urine to several liters a day. The administration of alcohol should be governed by the condition, for with marked toxæmia and great prostration alcohol is useful, and in such cases is probably best given as whisky in large doses.

Hydrotherapy, if possible in the form of the tub bath, should be carried out as in typhoid fever. In severe attacks it is well to give the tubs at a temperature of 70° F. In the patients with marked nervous symptoms it is well to use cold affusions to the head during the baths and an ice-bag or cold cloth should be kept constantly applied at other times. The use of antipyretic drugs does not seem wise. Delirium may require treatment and while the baths are usually the best means of combating this, it is sometimes difficult to give them. In this event one may have to substitute packs or sponges. Delirious patients should be constantly watched. With marked delirium, severe headache, or insomnia, it may be well to give bromides and opium, but in severe cases it is probably better to use morphia hypodermically. In the respiratory tract, careful attention should be paid to the condition of the nose and mouth and they may be irrigated or washed with an alkaline antiseptic solution. If signs of laryngeal involvement appear, the patient should be carefully watched so that if œdema of the glottis comes on, it may be recognized at once and tracheotomy done. The patients should be kept turned from side to side as much as possible to lessen the danger of hypostatic congestion. If there be failure of the circulation, strychnine may be given hypodermically (gr. $\frac{1}{40}$ to $\frac{1}{20}$, gm. 0.0015 to 0.003), digitalis, perhaps best in the form of digitaline hypodermically (gr. $\frac{1}{30}$, gm. 0.002), and camphor hypodermically (gr. ij, gm. 0.13), every two to four hours. Caffeine is also recommended. Conditions in the other organs must be treated as they arise. The bowels should be kept open by simple purgatives.

Convalescence is usually rapid but it is probably wise to keep the patient in bed for a week after the temperature is normal. If the pulse continues rapid or very slow, great caution is advisable and the patient should be kept quiet for some time, as in such cases there is always the danger of syncope. The return to work must be governed by the effects of the attack and the general condition.

CHAPTER VIII.

RELAPSING FEVER.

By THOMAS McCRAE, M.D.

This is a specific infectious disease,[1] usually occurring in epidemics, and caused by a spirochæte (known as the spirochæte or spirillum of Obermeier). The attack is characterized by fever, which usually lasts about six days, followed by a remission of about the same period, and then by a second attack of fever, and in some instances by a third, fourth, or even fifth.

Historical.—Long confused with other diseases, especially typhus and typhoid fevers, it was only in the early part of the last century that it was definitely recognized. The descriptions given by Rutty of epidemics in Dublin, in 1739–41, were probably of this disease. The distinction was probably first made in Ireland, in 1826, although in the epidemic of that date it was usually regarded as a mild form of typhus fever. In the next epidemic, in 1842, its characteristics were pretty clearly recognized, and Henderson, of Edinburgh, in 1843, held that the disease must be distinguished from typhus fever. Jenner (1849–51), and Murchison (1862), separated the disease and described its distinguishing features. In 1851 Griesinger observed the disease in Egypt, and described certain forms of it under the term of "bilious typhoid." In 1873 Obermeier discovered the cause of the disease, and since then there has been no confusion in its recognition. The disease has not been specially prevalent in Europe, although there were epidemics in Silesia, in 1848, in Russia, in 1863–64, and in Germany, in 1868. It has always been most prevalent in Great Britain, and especially in Ireland. In London it existed from 1869–71, probably having been introduced by Poles from Southern Europe. In America there have been few epidemics; in 1844 it was introduced into Philadelphia, probably by Irish immigrants, and the same source was responsible for epidemics in 1869, when the disease appeared in Philadelphia and New York. However, it never showed any tendency to spread among the American population.

It has occurred in Egypt and in other parts of Africa, but is much more prevalent in India, where there have been many severe epidemics. There have also been cases in the Philippines.

Etiology.—The conditions under which relapsing fever occurs are much like those favoring typhus fever. Poverty, overcrowding, deficient nourishment, and bad sanitary conditions, favor outbreaks. The contagion is communicated from one individual to another, and apparently this is by means of bloodsucking insects, ticks, etc., in some cases, at least. If the disease spreads from one district or country to another this is usually along the lines of travel. During epidemics the physicians and nurses have been very

[1]There are interesting papers by Carlisle, Norris, Paphenheimer and Flourney, and Novy and Knapp, in the *Journal of Infectious Diseases*, iii, 1906, No. 3.

frequently attacked. There is some evidence to show that infection may be conveyed by fomites, as clothing seems to have been the agent in some instances, and it has been noted that those handling the soiled linen may contract the disease. There are instances of the disease having been contracted by the handling of the bodies of those who have died of it. Season and climate do not seem to have any special influence. Any age may be attacked, but the majority of patients are between fifteen and twenty-five years. Sex does not seem to have any special influence except in so far that beggars and vagrants are more likely to be males. One attack does not give immunity.

The specific cause is the organism first described by Obermeier, of Berlin, in 1873, although he had observed it in 1868. It is often spoken of as a spirillum, although the term spirochæte is also used. This is a delicate, colorless, spirally-twisted organism like a fine thread of fibrin, its length being usually from two to six times the diameter of a red blood corpuscle. They may be found isolated or collected together in masses which have various appearances, and have apparently almost plugged the veins in some cases. It is apparently never quiet, and the motion is made up of rotation on the long axis, progression backward or forward, and the lashing movement. When found in the blood, it is easily seen moving about among the red corpuscles. No definite structure can be made out, although in some instances a granular or beaded appearance has been observed. These have been interpreted as spores, but are probably not. Cilia have been described by some authorities. Its presence in the blood is usually coincident with the attack of fever, and it usually disappears shortly after the crisis, although there are some variations, and it may be present in the blood after the crisis. The number of spirochæte found from day to day varies greatly, and they apparently sometimes vary periodically. As a rule they are few early in the attack, gradually increasing in number and reaching a maximum shortly before the crisis. They then decrease rapidly, and soon after the beginning of the sweating with the crisis have completely disappeared. The same conditions usually prevail in the relapse. The cause of the rapid disappearance of the organisms is unknown; high fever, phagocytosis, distinction in the spleen, and by bactericidal action, the development of a germicidal substance which inhibits their increase and finally causes their destruction. They do not seem to live long at the temperature of the blood, but much longer at a temperature of about 70°. Attempts to grow the organism on artificial media have not been successful. Novy and Knapp[1] have used collodium sacs filled with uncoagulated rat blood which were inoculated and then placed in the peritoneal cavities of rats. In these the spirilla increased in numbers, which suggests that they can multiply without any intracellular stage. The disease can be conveyed to another individual by inoculation with the blood of a patient taken during a paroxysm, and it has also been produced in monkeys by the same method. Certain insects, such as bedbugs, may suck out the spirilla, and in this way the disease has been given to monkeys. Mice and rats are susceptible to infection; rabbits and guinea-pigs are resistant.

It is possible that the disease may be caused by different varieties of spirilla. Novy and Knapp suggest that there are probably three relapsing

[1] *Journal of the American Medical Association,* Vol. xlvii, 1906, p. 2152.

fevers in man. The African form or tick fever is due to the *Spirillum duttoni*. The eastern and American forms may be due to different organisms. Novy and Knapp favor the bacterial rather than the protozoal nature of the spirillum, which name they also prefer to spirochæta.

Pathology.—There do not appear to be any characteristic findings in patients dead of the disease. The skin is sometimes yellowish in color, and may show petechiæ. If death has occurred directly from the infection the usual signs associated with death from an acute febrile disease may be found. The spleen is usually greatly enlarged, even to five or six times the normal, generally soft, and sometimes contains infarctions. The organisms may be found in it. The kidney, as a rule, is larger than normal, and the renal epithelium shows cloudy swelling. The changes of cloudy swelling may also be found in the liver, and the stomach and intestine may show catarrhal inflammation. The bone-marrow may show hyperplasia. In the bodies of those who have died from complications, other lesions have been found, as, for example, pneumonia and pulmonary gangrene. The spleen has sometimes been found ruptured, or an infarct may have broken down and set up peritonitis. The lesions of dysentery, which in some epidemics is a frequent complication, may be found.

Symptoms.—The period of incubation seems to be very variable. Some writers have reported instances of very short duration, while as long as fourteen days has been given; the average is probably from five to seven days. The average in animal inoculation experiments was ninety hours. During this period there are usually no symptoms; perhaps, exceptionally, general malaise. The onset is usually very abrupt and is commonly with a chill, while in young patients there may be vomiting or convulsions. There is generally a great deal of headache and giddiness, with pains through the body. The temperature rises rapidly and soon reaches 104° to 106° F. The pulse is almost always rapid, ranging between 110 and 140. The general condition rapidly grows worse and the patient usually goes to bed on the first or second day. As a rule the appetite is lost, though this is not invariable; great thirst is usually present. The headache continues and there may be marked insomnia. Gastric symptoms vary considerably; in some there is nausea and vomiting of greenish fluid, while pain with tenderness on pressure is often found in the upper abdomen. The liver is usually somewhat enlarged, and the spleen markedly so, the edge often projecting below the costal margin; both may be tender. Jaundice is not infrequent, usually appearing about the third or fourth day; its frequency varies greatly in different epidemics. As a rule there is bile present in the fæces. There is often a polymorphonuclear leukocytosis.

The face is flushed and the eyes injected, but delirium is rare, and the expression is usually natural. Severe muscular pain is frequently present. Rashes occur occasionally; herpes have been noted, and rarely a roseolous or mottled rash something like that of measles. Sudamina may be present in large numbers, and petechiæ are not uncommon. As a rule the skin is very dry; some patients have profuse sweating which may last for hours. In an ordinary attack the condition changes but little for about a week. The pulse and temperature remain high, the patient suffers from severe headache and pains through the body, and is often troubled with sleeplessness. There may be slight delirium toward the end of the first week. Usually on the fifth or seventh day there is a sudden subsidence of the fever. This may occur

as early as the third day or be delayed until the tenth. The crisis usually appears at night, and just before it there may be temporary delirium, epistaxis, or diarrhœa; but the most constant feature is profuse sweating. With this the temperature falls to normal in a few hours, and may drop from eight to twelve degrees. With this the pulse drops to a normal rate and the pain disappears; pseudocrisis is sometimes seen. During the crisis or shortly before it the spirochæte usually disappear from the blood.

For a short time after this, the patient may feel rather exhausted, but as a rule strength is quickly regained, and he may insist on going back to work. The temperature for two or three days is usually subnormal, and the pulse sometimes drops below the usual rate. After a week or even twelve to fifteen days of normal temperature, the second attack usually comes, although in some epidemics 30 to 40 per cent. of the patients had only one attack. The second attack is usually shorter than the first, although in some the relapse is worse, especially if the first has been very mild. The spirochæte reappear in the blood. If the second attack has been severe it usually terminates by a crisis just as the first. After this the patient usually passes on to complete recovery; but sometimes there is a third attack, or even a fourth or fifth. As a rule convalescence is slow and strength is regained very gradually; but this depends largely on the number and severity of the attacks.

Complications are not very common, pneumonia being the most frequent. In cases with severe jaundice, the patient may sink into a typhoid state and gradually die. It was to such that Griesinger gave the name of "bilious typhoid." The occurrence of jaundice varies greatly in different epidemics. Hemorrhage from the stomach occurs, and in some instances the very large spleen has ruptured; in others an infarct of the spleen has broken down and set up peritonitis. Dysentery occurs in some epidemics, and may prove fatal. Acute nephritis has been observed. When the disease occurs in a pregnant woman, delivery almost always occurs, although this may not be until the relapse. If the pregnancy has been advanced and the child be alive at birth, it usually dies. Inflammatory parotitis or adenitis has been noted in some epidemics. Ophthalmis has occurred. Complications in the nervous system are not common; hemorrhagic pachymeningitis has been observed, and paralyses may occur. After the disease is over there may be much trouble from articular pains, and effusion into the joint has been seen. Ophthalmia when it occurs is usually a sequel; this usually affects only one eye, and sometimes results in loss of sight. Relapsing fever may co-exist with other diseases, such as malarial, typhoid, and typhus fevers, diphtheria, smallpox, measles, and scurvy.

Relapsing fever, as a rule, is not very dangerous; Murchison estimated the mortality in Britain and Ireland as about 4 per cent.; but in India Carter has stated that it sometimes rises to 10 per cent. In one epidemic in St. Petersburg the death-rate was 12 per cent. Death from the disease itself may be owing to the severity of the toxæmia or to sudden collapse, very often at the time of crisis, as is especially apt to occur in older people. Apart from this, death is usually due to one of the complications, such as pneumonia.

Diagnosis.—This is likely to present difficulty only early in the attack, but the sudden onset, high fever, rapid pulse, the rapid increase in the size of the liver and spleen, and the general muscular pains, should be suggestive. During the first forty-eight hours it may present features like many of the other acute infections, especially typhus fever and smallpox, while mistaking

it for typhoid fever is a possibility. In other instances it may be confounded with yellow or malarial fever. If jaundice be frequent there is a possibility of mistaking it for Weil's disease. During the course, however, there should be no difficulty whatever, as the examination of the blood should show the spirillum. In the absence of this, the typical relapsing character of the fever should be sufficient.

Treatment.—Until we are sure of all the methods of transmission, the patient should be isolated and the ordinary rules for the handling of infectious diseases carried out. If it break out in an unsanitary district the houses should be inspected every day to recognize the early cases. As regards the patient, we have as yet no specific treatment nor any means of cutting short the fever or of preventing a relapse. Quinine, arsenic, carbolic acid, preparations of chlorine, etc., have been tried without results. The patient should be put to bed, given a liquid diet, and hydrotherapy used, probably best in the form of sponges. If the fever be very high, tub baths may be used, especially the gradually cooled bath. During the fever the bowels should be kept open by castor oil or a mild purgative. For the headache and the various muscular and arthritic pains, chloral hydrate may be given or, if necessary, opium. Rubbing with chloroform liniment has relieved the pains in the limbs. In patients of advanced age it is well to give stimulants, especially about the period of the crisis. Complications should be treated symptomatically. If there has been a previous nephritis it may be well to give a diuretic mixture throughout, along with large amounts of water.

The African relapsing fever depends largely on the bites of ticks; and pitching camps on grounds not used before is an important prophylactic measure. In epidemics the patients should be removed to places free from vermin, and every effort made to destroy bedbugs, ticks, etc., as well as to avoid their bites.

CHAPTER IX.

SMALLPOX.

By WILLIAM T. COUNCILMAN, M. D.

Smallpox (Latin, Variola; French, la Variole; German, Blattern or Pocken; Italian, Vajuola) is an acute infectious disease characterized by a sudden onset, an initial stage of three days' duration which is followed by a cutaneous eruption of vesicles and pustules which are seated within the epidermis. After recovery the seat of the cutaneous lesions is marked by cicatrices whose extent and depth depend upon the character of the pustules. Variola is the most characteristic of the acute exanthemata, and in no other disease in man do the various stages succeed one another with such regularity. This is apparent in the literature, for the clinical descriptions of the disease from Sydenham down to the present time present great uniformity, and there has been but little added to the description given by him two hundred and fifty years ago. Smallpox is highly infectious, and no immunity is given by race, sex, age, or season. Notwithstanding this, so great is the protection given by vaccination that a large majority of physicians have never seen a case of smallpox, and in civilized lands we rarely see an individual bearing the cicatrices produced by the disease.

History.—It is probable that smallpox has prevailed in the human race from remote antiquity. The first description of the disease which leaves no doubt as to its nature is given in the well-known treatise by Rhazes, in the tenth century. It is evident that he did not regard it as a new disease. He discusses chiefly the causes and mode of treatment, and refers only incidentally to the lesions. The cause he ascribes to a too rapid fermentation of the blood, and compares the pustules to the gas bubbles formed in fermenting must. His regimen and treatment are in the main good and harmless, and might with advantage have been substituted for the treatment followed up to the time of Sydenham. It is, however, remarkable that Rhazes makes no mention of the contagiousness of the disease, nor of the fact that one attack confers immunity. In the writings of Galen there are no specific descriptions of smallpox, though Rhazes assumes that he knew the disease. It is possible that the pestilences which swept through the Roman Empire in the time of Antoninus (A. D. 160–68) were smallpox, and, also, the disease which ran through the greater part of southern Europe in 580. There are undoubted statements as to the presence of smallpox in Europe during the eleventh and twelfth centuries, and the tumultuous movements of the people during the crusades undoubtedly contributed to its spread.

No region can be found from which the disease originally spread and which can be regarded as its home. There are at present regions in Asia and in central Africa where smallpox is endemic and uncontrolled by vaccination. From these centres it has been many times conveyed to other lands, particularly during the slave-trade. Many outbreaks of the disease in America can

be traced directly to the importation of African negroes. The conditions now found in central Africa must have generally prevailed in the prevaccination period. In the absence of frequent intercommunication it was possible for the disease to become extinct in a small community. Widespread epidemics were generally due to war or other conditions which led to increased intercommunication.

The disease reached its highest point in Europe during the eighteenth century. No country was free from it, and with the subsidence of the bubonic plague, smallpox became the dominant disease. In England deaths from smallpox formed one-tenth of the entire mortality; in France 30,000 died of it yearly; and in Prussia alone in one year (1796) there were 26,646 deaths. In this terrible time war, by increasing communication, by producing poverty followed by numbers of strolling beggars and the movement of idle population, was the chief cause of the prevalence. War caused more havoc by disseminating disease than by fire and sword. The period of universal prevalence extended well into the nineteenth century, causing great havoc, particularly in Russia, where the deaths have been estimated as high as 10,000,000. The disease became preëminently one of childhood, nearly all adults being protected by a previous attack. It attacked both high and low, prevailing equally in the houses of the rich, the tents of the army, and the hovels of the poor.

The discovery of Jenner came at the most opportune moment. It is impossible to overestimate the influence which that has exerted in furthering civilization and the physical and moral advance of the human race. Without vaccination and with the present intercommunication, smallpox would be a pandemic raging over the entire world. It would certainly still the fears of those who dread an excess of population. At the present time the disease is chiefly seen in the most ignorant and wretched of the population, the strollers who do not acquire a residence so as to be subject to vaccination laws, and the criminals who evade the laws. The disease is also kept up by a class of people who are either ignorant or have a peculiar order of mind which renders them incapable of sane judgment and who seek in every way to oppose vaccination. The saddest feature is that in every epidemic there are a number of unvaccinated children in no way responsible, who either die of the disease or are permanently disfigured.

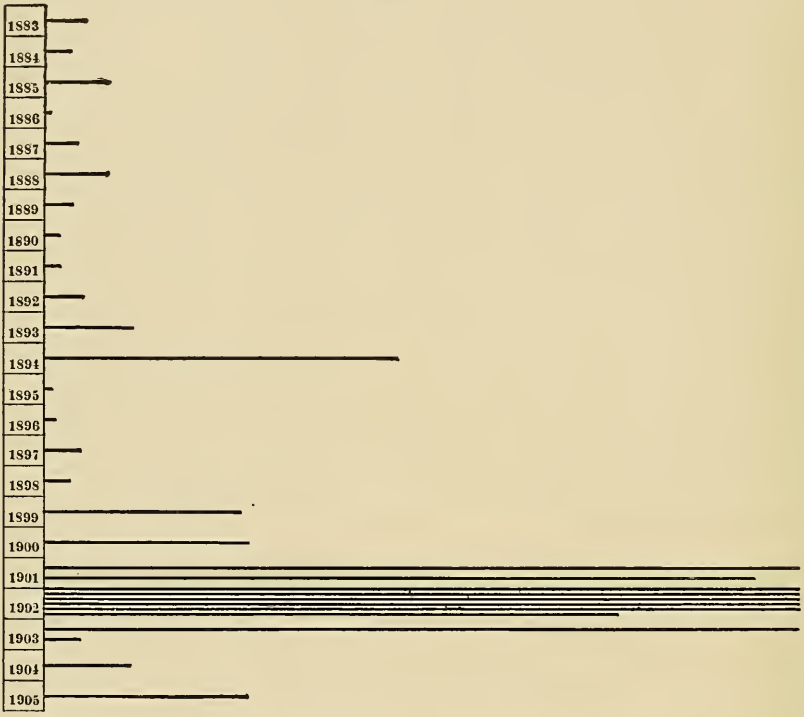
Incidence.—None of the acute infectious diseases shows such a complete independence of the conditions of race, climate, and soil, as does smallpox. It thrives equally well wherever its contagion is carried and where it finds a susceptible population.

The susceptibility of the population varies. During and after each appearance of smallpox in a community, vaccination is carried out more vigorously and the susceptibility is diminished or rendered *nil* by vaccination or an attack of the disease. With the passing of the disease, vigilance relaxes and the number of susceptible individuals increases. The disease is kept alive by sporadic cases, which furnish the virus, and with this and susceptible material there will be an outbreak. There is an irregular periodicity in the recurrent outbreaks of the disease. Thus in Massachusetts the number of cases from 1883 to 1905 were for each year as follows—shown by the following chart. (Fig. 13.)

The epidemics in the prevaccination period show the same irregular periodicity. In Boston there were epidemics varying in extent in 1649, 1666, 1678, 1690, 1702, 1721, 1730, 1752, 1764, 1788, and 1792.

The season of the year has an influence on the morbidity and upon the diffusion of the epidemic. Rhazes says that in Arabia epidemics occurred at all seasons, but generally began toward the end of autumn, or in the early spring, or in the cold season. Hirsch gives the following table showing the period when the disease was at its height in 99 epidemics in Europe or North America of which there are accurate data:

Fig. 13.



Cases of smallpox in Massachusetts from 1883 to 1905. 2½ mm. of the lines equal 10 cases.

Autumn and winter	10
Winter	17
Winter and spring	16
Spring	24
Total	67
Spring and summer	7
Summer	14
Summer and autumn	6
Autumn	5
Total	32

Even here there is much irregularity. In England, for instance, between 1837 and 1840 there were in the winter 9,095 deaths, in the spring 9,470, in

the summer 10,005, and in the autumn 12,483. The epidemics in America of 1882 and 1902 reached their greatest extension in the winter and early spring. The following curve shows the influence of season on the disease in the last outbreak in Massachusetts, from 1901 to 1903:

Fig. 14.

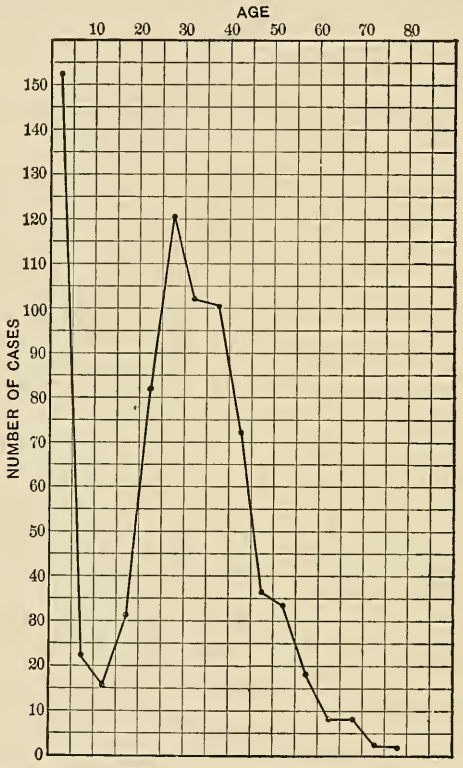
The dark lines represent the number of cases of smallpox in Massachusetts for each month in 1901, 1902, and 1903. The dotted lines represent the deaths. Notice the great decline in mortality at the end of the epidemic. 2½ mm. equal 10 cases.

The mortality seems to be greater during the height of the epidemic than at its decline, as is shown by the chart. The mortality, however, varies greatly in different epidemics, this being true both of the prevaccination era and now. In 1901 to 1903 there were epidemics in various parts of the United States in which the mortality was as low as 2 per cent. The mortality in the epidemic seen in Philadelphia is given by Welch and Schamberg as 26.89 per cent. in the 7,204 cases. In Massachusetts in the years mentioned it was 11 per cent. It is not certain that children are naturally more susceptible to the disease than adults. The cases among them decrease in frequency after the tenth year, owing to vaccination when they enter the schools. This is shown in the table of ages (Fig 15) of 800 consecutive cases in Boston.

The mortality under one year is always high because practically no vaccinated cases are found.

Race seems to exert little influence either on morbidity or mortality. When the disease is introduced into aboriginal tribes the mortality is extremely high. The first outbreak of smallpox in the Western hemisphere took place in the West Indies, in 1507, fifteen years after the discovery of America, and was so disastrous that whole tribes were exterminated. The complete disappearance of the Lucayan Indians is to be chiefly attributed to smallpox.

FIG. 15.



Curve of ages of 800 cases of smallpox. Notice the extraordinary decline at 8 years. (School vaccination.)

The disease reached Mexico in 1520, with troops from Spain, and the number of persons destroyed in a short time has been estimated at three and a half millions. In the epidemics in this country, cases are always relatively more numerous among the blacks, and the mortality is higher. Both the increased morbidity and mortality are due to the greater percentage of unvaccinated among the blacks. Welch and Schamberg found the mortality in unvaccinated cases 49.45 per cent. in the blacks and 44.69 per cent. in the whites.

Etiology.—Bacteria were first found in the organs of smallpox cadavers by Weigert, in 1874. Since that time both cocci and bacilli have been found by various observers in the specific lesions, and by some have been regarded

as the cause of the disease. All of these bacteria have been shown to belong either to the ordinary pyogenic cocci or to be forms of bacilli common to the skin. It is now generally believed that these bacteria are accidentally present or are secondary invaders, and though they may play an important part in the pathology of the disease they have no bearing on its specific etiology. No bacterium has been found peculiar to the disease and occurring nowhere else; in many cases it is not possible to demonstrate bacteria either microscopically or culturally in the specific lesions; when bacteria are found they are present in the advanced lesions rather than in the young and developing lesions. Lesions peculiar to the disease have not been produced by inoculating animals with pure cultures of the various bacteria found.

The included bodies in the epithelial cells of the lesions, which have played an important role in the later attempts to discover the etiology, were first described by Weigert, in 1874. There inclusions were first regarded as parasitic by Renault, in 1881. Guanieri, in 1892, gave the first clear description of the bodies which he regarded as parasitic protozoa and the cause of both vaccinia and smallpox. In his first publication he describes bodies which stain with carmine, hematoxylin, and safranin, in the deep-lying epithelial cells of the skin in vaccinia and smallpox pustules, as well as in the epithelial cells of the cornea of rabbits which were inoculated with either vaccine or variola virus. He found the bodies lying in clear spaces adjoining the nuclei of the epithelial cells, and varying in size from that of a micrococcus to that of the nucleus of a cell. He gave the organism the name of "*Cytorhyctes variolæ*," the name having reference to the supposed property of the organism of devouring the epithelial cells and in this way forming a space within which the organism lies.

Since the publication of Guanieri, a number of articles with reference to these bodies have appeared, which have been, in the main, confirmatory of his description and interpretation, but which with few exceptions have added little to our knowledge of their more intimate structure or nature. Up to 1904 the most important article confirmatory to the views of Guanieri was that of Wasielewski, in 1901. He also regarded the bodies as parasites and the cause of the disease. The organism enters the epithelial cells, and its first influence is to produce an increased nutrition and enlargement of the cell. He showed, further, that no other injury to the cornea of the rabbit and no other form of infection produced lesions of the same character as those produced by inoculating the cornea with vaccine or variola virus. In the lesions he always found these bodies and no other foreign structure. The bodies, very small in the earliest lesions, became large, and with the increase in size came a further differentiation of structure. He showed that the virus increased in the lesions for he could inoculate from eye to eye indefinitely without any change in the character of the lesions. He inoculated from the cornea of the rabbit to the calf in the fifteenth and twenty-fifth generations, and in each obtained perfectly typical vaccine pustules and immunity to further vaccination. Children were vaccinated from the cornea of a rabbit in the thirty-sixth generation, and typical vaccinia resulted.

There have also appeared a number of articles which oppose the views held as to the parasitic nature of these bodies which are included in the epithelial cells of the lesions. By some the bodies are regarded as the products of degenerations in the epithelial cells; by others as leukocytes which have become included in the cells; and by still others as red blood corpuscles.

In the studies which were carried out on smallpox and vaccinia in 1902 and 1903 by Councilman and his co-workers, these bodies were unqualifiedly regarded as parasites and the cause of the disease. In the course of the work important additions to our knowledge of the structure of these bodies, their cycle of development, and their etiological significance, were made.

In the skin lesions of smallpox, and particularly in the earlier stages, certain small bodies are seen in the epithelial cells. These bodies show a variation in size, external form, and internal structure. The smallest are less than 1 μ in diameter. They lie usually in a vacuole of the cell close to the nucleus, and usually but a single body is found in a cell. Occasionally two are found lying on opposite sides of the nucleus, and in rare instances they have been found between the epithelial cells. The appearance of these bodies is coincident with the earliest changes in the epithelial cells. They may be found in cells which show no other change, and in cells whose nucleus is dividing. When first seen, these bodies are refractive and homogeneous in the unstained specimens, and stain slightly with most staining reagents. From such forms there is a progressive development (Fig. 16). They enlarge and preserve their homogeneous character, remaining round or oblong until they reach the size of 4 to 6 μ. At this stage clear spaces appear in them, and in the middle of the clear space a small dot, which in specimens stained with methylene blue and eosin usually stains blue, while the remainder of the body assumes a reddish tint (Fig. 17). With the increase in size of the body, the degeneration of the cell enclosing it progresses and the enclosing space enlarges. The body continues to increase in size until it becomes as large or larger than the nuclei of the epithelial cells. It no longer preserves its round or oval sharp outline, but becomes elongated, irregular, and sometimes assumes an hour-glass form. The structure increases in complexity, and shows, finally, small round bodies enclosed in a reticulum. The reticular structure breaks up and the enclosed small bodies lie free in the vacuole of the cell. The vesicle of smallpox develops from a single point in the skin, and from this there is extension in all directions to a variable extent. In early vesicles it is possible to recognize

Fig. 16.

Section of the lower part of the epidermis showing the cytoplasmic stage of cytoryctes in the epithelial cells. ×1000.

Fig. 17.

Two of the larger cytoplasmic forms of cytoryctes in the epithelium. The two dark bodies in the middle showing reticular structure are the parasites. ×1000.

a central older area and a peripheral area of extension. In the oldest area the most developed of the cytoplasmic inclusions are found, and in the periphery the smallest and presumably youngest forms. The conclusion is inevitable that the progressive development of the vesicle is due to an increase of the virus and its dissemination in the surrounding epithelial cells.

Inclusions in the cytoplasm of the cells only are found in the earliest lesions. In the late vesicular stage and in the beginning pustule, new structures begin to appear in the nuclei of the epithelial cells in the centre and oldest portion of the lesion in which the cytoplasmic inclusions have disappeared. The nuclear inclusions begin with the appearance of one or several small circular masses in the nucleus. These have a sharp outer rim and a clear homogeneous refractive content. They increase in size, and with growth show a greater complexity of structure. The form varies; at times the entire structure appears to be composed of an infinite number of small circles, in the centre or at the side of which small stainable points can be made out. In other cases there is a large central space around which are grouped a great number of very small spaces all bearing the central dots (Figs. 18 and 19). The nucleus enclosing these bodies enlarges, the central chromatin disappears, leaving only a thin, faint, nuclear rim, which finally disappears, the enclosed bodies are set free, and they may be found in the central mass of broken-down cells, mixed with exudation. In the degenerated nuclei there are often found small, refractive, brightly staining points measuring less than 0.5μ in diameter.

In all vaccine lesions which we have studied, whether in man, in monkeys of various species, or in the calf or rabbit, bodies essentially similar to those included in the epithelial cells in smallpox in man, and undergoing the same changes and development, are found. There is no difference in the size, relative numbers, and course of development, of these bodies, whether the tissue chosen for the site of vaccination be skin, mucous membrane, or cornea. All competent observers agree in this. If the rabbit or calf be similarly inoculated with material from smallpox lesions in man, a lesion is produced which is essentially the same as that produced by vaccination, and the same inclusions are found in the epithelial cells. The results of the two processes are in all respects the same, and immunity from both smallpox and vaccinia is conferred. It is known that many of the strains of vaccine lymph have been derived from the calf by inoculation with smallpox virus. Neither the calf nor any other of the domestic animals is susceptible to smallpox. The disease which they acquire by inoculation with smallpox virus is vaccinia.

Neither in man nor in the monkey, nor in any other animal experimented with, are the nuclear bodies found, when vaccine material is used for inoculation. Typical vaccine lesions without general eruption are produced and only the cytoplasmic inclusions are found in the lesions. The same is true of the rabbit and calf when smallpox material is used for inoculation. When smallpox material is inoculated in the monkey, after an incubation period of about eight days there develops an exanthem, varying in extent, and differing in nowise, save in being less extensive, from the exanthem of smallpox. In the lesions of this, the nuclear inclusions in the same form and undergoing the same development are found along with cytoplasmic forms. Inoculation of the smallpox exanthem from monkey to monkey results in smallpox with exanthem and with nuclear bodies. Inoculation from the monkey with smallpox to the rabbit results in vaccinia without the nuclear

Fig. 18.

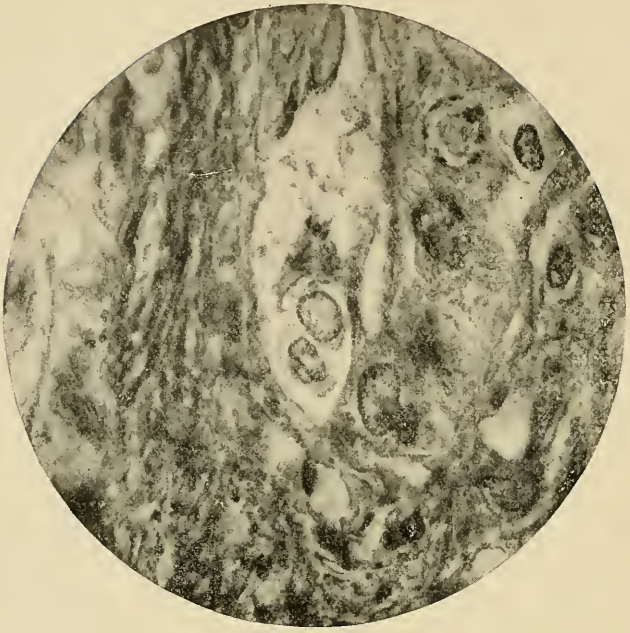
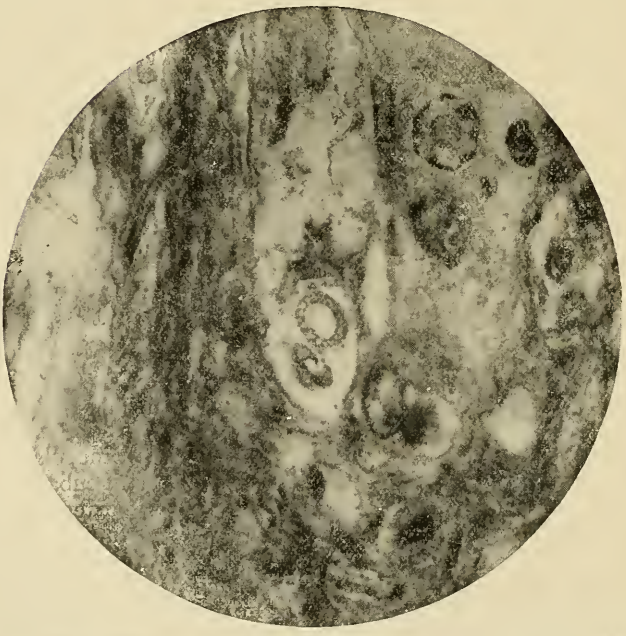


Fig. 19.



Free-lying intranuclear parasite with adjoining nuclear fragments. In Fig. 18 the surface view is given; in Fig. 19 the optical section through the centre.

inclusions. These bodies within the nuclei are characteristic of smallpox. It has seemed to us from this that the organism in smallpox and in vaccinia was the same, that in vaccinia it only reached a degree of development comparable in a general way to the asexual self-infecting cycle of the malarial organism; that in smallpox, however, in addition to this development, which takes place in the cytoplasm of the epithelial cells, there is a further development, comparable to the sexual cycle of the malarial organism which takes place within the nucleus. Calkins, who has worked on material from smallpox cases in this epidemic, has from the series of forms found in the lesions projected the following provisional life-history:

"The first development of the germ in the host is unknown. It probably takes place in the seat of primary infection, forming an organism which reproduces by germs, probably similar to those which I have named gemmules (*i.e.*, the small bodies ultimately formed in the cytoplasmic inclusions), the process being known as 'multiplicative reproduction.' The gemmules are probably carried in the blood to the skin, where the further development takes place. This early part of the development therefore is purely conjectural, but from this point the observations are fairly complete. The gemmules become intracellular cytoplasmic amœboid organisms which give rise to similar gemmules. This process, which Councilman has designated the 'vaccine cycle,' must continue for some time, for in variola the gemmules are distributed to all parts of the skin. Ultimately the germs derived in this way give rise to forms which penetrate the nuclear membrane and develop into gametocytes (?) of two types, one forming the supposed male gametes, the other the female. The gametes conjugate (?), the zygote thus formed develops into a comparatively large, amœboid organism, in which the pansporoblasts originate. These pansporoblasts give rise to primary sporoblasts, and the latter to multitudinous spores, the entire process taking place within the nucleus and corresponding to the so-called propagative reproduction of other sporozoa. The spores thus formed may, in turn, infect fresh nuclei and grow directly into new, secondary sporoblasts, which give rise to similar spores, a true schizogony and a second means of auto-infection, by which the organism spreads throughout the nuclei and cells of the skin, and possibly to many of the other organs of the body like the allied *Nosema bombyces*, which infects every tissue and cavity of its insect host. These spores finally may transmit the disease to new hosts."

We have regarded the small spore-like bodies found in the skin lesions in the later stages as probably representing the final spores which are the true agents of infection in smallpox. There is one very striking difference in the manner in which infection takes place in vaccinia as compared with smallpox, and which is only to be accounted for by differences in the character of the infecting agent. Infection takes place in vaccinia only when the virus is placed in contact with suitable epithelial cells of the skin or mucous membranes. Infection rarely takes place in any other way than by design, though there are cases of accidental infection by means of intermediate objects. Infection in vaccinia does not take place by air transmission and does not follow from patient to patient. In smallpox there are a large number of observations which show that infection can and usually does take place by air-borne infectious material. There are many observations which show that infections can take place across wide areas. The most convincing evidence of the air transmission is given by W. H. Powers (in the Local

Government Board Reports 1880–81, also 1884–85), who showed that a smallpox hospital can serve as a focus of infection for the vicinity. Both Barry and Evans, the former from his observations at the Sheffield Hospital in the epidemic of 1887–88 and the latter from observations in the epidemic at Bradford, come to the same conclusions. The direction of the prevalent winds has a decided influence in extending the infection. In addition to the influence thus exerted by hospitals, there have been instances in which the disease has extended from a completely isolated individual in a house to other rooms of the house by means of the open windows.

The spore-like bodies which form the infectious agent in smallpox have widely different characters from the gemmules which form the infectious agents in vaccinia. In some respects the comparison of the smallpox infecting agent to the spore is not borne out. Thus Brinckerhoff and Tyzzer have found in their comparison between the resistence of the smallpox and vaccine virus to external conditions, that the vaccine virus is more resistent than the smallpox virus. Assuming these two cycles of development, if the smallpox spores be inoculated on the calf or rabbit, in the tissues of these animals favorable conditions are found for the development of the primary vaccine cycle but not for the smallpox cycle. The virus growing in these animals loses after a variable period its capacity for complete development, and true vaccinia is produced and transmitted. How long a period elapses before the capacity for variola is lost is unknown; in one case after the variola virus has been passed from the cornea of rabbit to rabbit for four generations, inoculation of a monkey from the last generation produced an initial lesion showing the characteristics of variola and followed by an exanthem.

Pathological Anatomy.—The majority of autopsies in smallpox will be made on patients who have died between the tenth and twelfth day of the disease, with the skin lesions in the late pustular and crusting stage. It is possible in the cadaver from the character of the eruption to determine roughly the stage of the disease. In the earliest cases the lesions consist of papular elevations 2 or 3 mm. in diameter, very slightly raised above the level of the skin, so hard that they give to the finger the sensation of a small shot. The lesions are generally most numerous on the forehead, cheeks, neck, shoulders, the upper part of the chest, the backs of the hands, and the inside of the thighs; they are sparse on the abdomen, particularly on the lower part. The lesions are not distinctly vesicular on the cadaver until the fifth day. Toward the close of the first week the lesions on the face may become confluent. The face is œdematous and the nostrils covered with crusts. In children there is a tendency for the lesions of the legs to appear in groups, and they also differ in size.

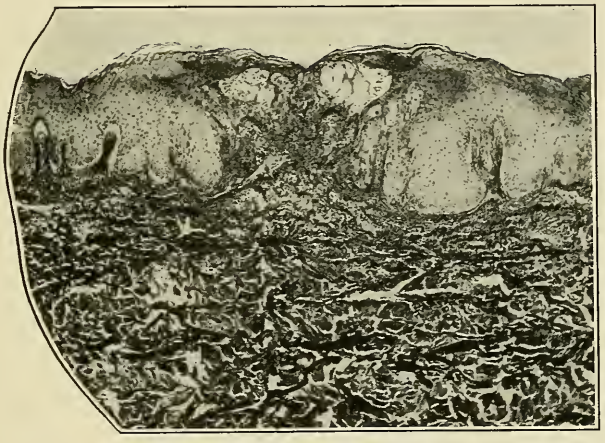
In patients dying in the distinctly lethal period of the disease, the face shows great œdema and is covered with crusts which in size and extent depend upon whether the pustules were discrete or confluent. The crusts may cover the face and neck like a mask. The skin of the trunk shows intact pustules interspersed with occasional ruptured pustules and crusts. The axillæ, flanks, and groin, are usually devoid of lesions. Upon the arms the lesions are more abundant on the extensor surfaces and on the backs of the hands and wrists than elsewhere; they may be confluent, and large blebs filled with serous fluid may be formed. Palms which possess a thick horny layer of epidermis show lenticular copper-colored disks;

those of children and others, in whom the epidermis is thin, may show pustules.

In the third week of the disease and later, the skin of the face is marked by copper-colored or reddish areas, at first more or less elevated and scaly, later becoming colorless pits. The skin of the trunk and extremities shows markings of a similar character which gradually lose their color. After the falling off of the crust, the sites of the lesions are somewhat elevated and rough. The palms and soles usually show reddish-brown disks, the color depending upon the thickness of the epidermis.

In purpuric smallpox the skin of the face shows a dusky bluish-red flush, deepest about the neck and ears. The skin of the trunk presents a general terra-cotta or bluish-red flush, deepest upon the dependent parts. The specific eruption may be absent or represented by a few scattered papules or vesicles. The epidermis, even a short while after death, strips off readily in large sheets, leaving a moist, glistening surface.

Fig. 20.

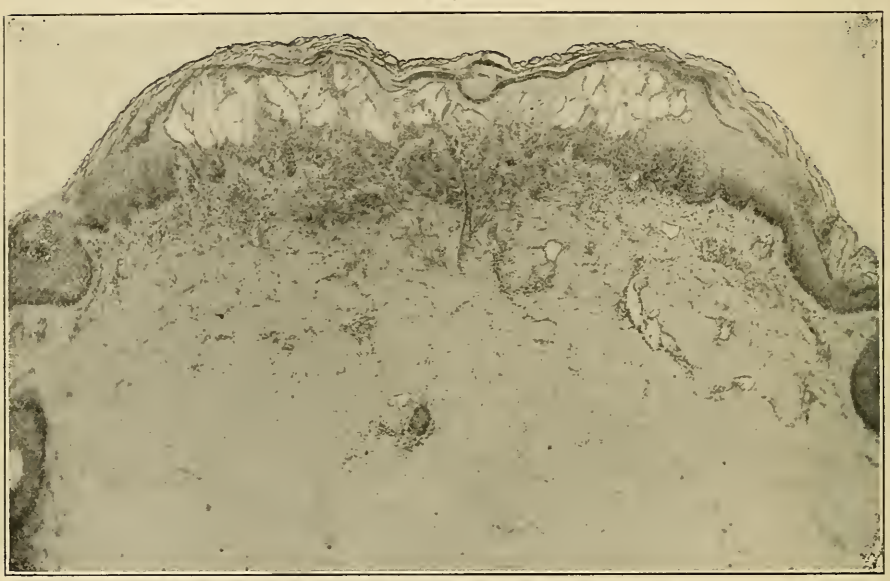


Small beginning vesicle. × 24.

For the study of the development of the pustule it is necessary to observe a large number of cases. It is not often that the earliest stages of the papule can be seen. The factors concerned in the production of the pustule are degeneration of the epithelial cells and exudation into the degenerated part. The beginning of degeneration is seen in the nuclei of the epithelial cells. The nuclei are swollen, more vesicular, and the clumping of chromatin in the centre more marked than in the normal. Associated with this nuclear change is a reticular degeneration of the cytoplasm which may affect all the lower cells of the epidermis. The cells are swollen; the cytoplasm loses its normal character and becomes either a faintly stained pale mass, or distinct spaces may be formed in it. The protoplasmic processes connecting the cells disappear and the cell periphery undergoes a peculiar condensation. With the increasing exudate coming from below, the spaces within the cells enlarge, finally rupture, and a net work or system of spaces is formed by the coalescence of the cell-borders. The typical small vesicle is always fan-shaped (Fig. 20). The bottom of the vesicle may be seated on the corium

or be separated from this by a layer of comparatively intact cells The lowest epidermis cells undergo a hyaline fibrinoid degeneration and form the handle of the fan. Above this and extending widely laterally is the reticular degeneration leading to the formation of spaces. The cells of the keratohyaline layer of the epidermis take but little part in the formation of the reticulum, though they may be separated by the exudate. As the exudate increases, the tension becomes so great that the adherent cell-remains are ruptured, and large spaces are formed with the cell strings extending irregularly between them (Fig. 21).

Fig. 21.



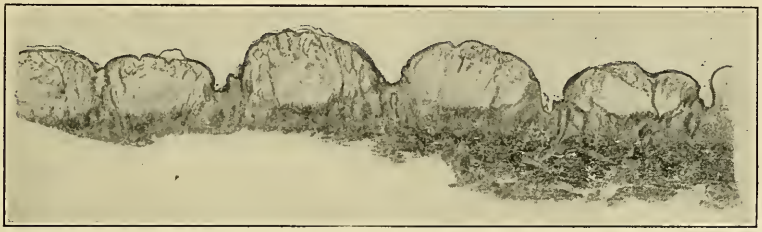
A more advanced and larger vesicle than in Fig. 20, showing the internal mesh-work formed by the remains of the epithelial cells.

In the hyaline fibrinoid degeneration the cells become swollen, their protoplasm loses its granular character, becomes homogeneous and refractive, and stains more intensely with the acid dyes. The single cells so altered may be separated from each other, or masses of them may be joined together and lie more or less free in the exudate. The direct division of the degenerated nuclei of these cells is not uncommon, and four or more pale nuclei formed in this way may be found in a single cell (Fig. 22).

The exudation begins early and in most cases simultaneously with the cell degeneration. In the smallest visible papule the swelling is chiefly due to exudation. The earliest visible lesion of the skin is really a vesicle, but the exudation enclosed in a number of small spaces does not give the swelling the macroscopic appearance of a vesicle (Fig. 20). In the early stages the exudate is clear, without any admixture of cells, and may be very poor in coagulable constituents. Leukocytes only appear in the exudate in a late stage and when the specific character of the process has passed, then being attracted by the necrosis. In a late stage of the pustule all the cells, both those in the exudate and the degenerated epithelium, become frag-

mented and give rise to granular masses which cannot be identified. One form of degeneration of the polynuclear leukocyte is particularly noticeable. The cell becomes swollen and clear, the granular contents disappear, the nucleus is swollen, and the chromatin is arranged in small masses (often of the same size) at the periphery of the nuclear membrane, in some cases assuming the form of rosettes. Red blood corpuscles are rarely found in the exudate in the young vesicles, but a few may be found in the pustules. Eosinophile cells in any numbers were rarely found either in the exudate in the vesicle or in the pustule, or in the corium, except in one case, that of an infant. The diminution in the number of polynuclear leukocytes in the blood cannot account for the small numbers of these found in the skin lesions, for in the lesions in the lungs and mucous membranes, which are due to streptococcus infection, the exudate has the usual cellular character.

FIG. 22.



A number of contiguous vesicles in the skin of a child, eighth day. The two on the left are con fluent. Observe the irregularity of the umbilication and the appearance of umbilication resulting rom confluence.

The bloodvessels of the corium are injected both immediately beneath and in the vicinity of the lesions. There is extensive hemorrhage in the corium in the purpuric cases and to a less degree in the simple hemorrhagic cases. In the purpuric cases the hemorrhages are not circumscribed but diffuse.

The histological examination of the skin in purpuric smallpox removes all doubt as to the nature of the disease. The skin almost everywhere shows the earliest stage of the true lesions. Often the entire area of a large section shows the same condition, or only small areas of normal skin are found. The general condition is swelling and reticular degeneration of all the lower cells of the epidermis. There are large vacuoles in the cells, but rarely spaces between the cells resulting from the rupture of the vacuoles. The nuclei of the cells are degenerated, shrunken, and lie in large spaces. In the cells least changed the chromatin of the nucleus is clumped in the periphery. In all the purpuric cases the writer has examined there were large numbers of streptococci in and around the vessels.

Bacteria are generally absent in the microscopic examination of both vesicles and pustules. In the examination of many sections of the skin from 54 cases they were only found in 6 cases. Cocci, usually in chains or in pairs, were the form of bacteria found. In one case it seemed possible that the skin might have been the point of invasion for a general septicæmia. The bacteria are found more frequently in the corium than in the epidermis. They are usually seen as embolic masses within the vessels and occasionally in the tissues around the vessels. They are not found more frequently nor in greater numbers in the vessels of the corium than in the vessels of any other

part of the body. In no case are they found in such relation with the early epithelial lesions that they can be considered as a causal factor.

The examination of the skin strongly suggests that the specific organisms are brought to the skin by the blood. They enter into the epithelial cells at a single point, and from this the formation of the lesion extends. The essential difference in purpuric smallpox is that the organisms reach the skin in great numbers, so that large areas of the epidermis may show the conditions which ordinarily are found only at the primary focus of the vesicle formation.

Repair of the lesion begins early. In an early stage of vesicle formation there is slight hyperplasia of the surrounding epidermis and the horny layer is thickened. The newly formed horny cells are œdematous and swollen, and their nuclei are faintly visible. The contents of the vesicle or pustule undergo condensation, becoming finally converted into a solid granular mass. In the less severe cases the destruction of the epithelium is not complete, and there may be rows of cells at the bottom of the lesion which are little or not at all affected. New epithelium is produced by these cells, or grows from the sides beneath the outlaying edges where the process does not extend to the papillæ. In large pustules with degeneration involving large areas of the skin with destruction extending deeply into the corium, the growing epidermis is always found at the edge. All layers of the skin are not formed simultaneously in the regenerative process. The cells of the horny layer are formed in great numbers in the periphery of the lesion and from this gradually extend over the deeper cells which have already been formed. By means of this regeneration the mass of cells and exudation in the lesion, which has become solid by evaporation and absorption, becomes enclosed within two layers of horny cells—the old layer which formed the surface of the pustule and a lower layer which is newly formed. Complete regeneration without cicatrization is possible when the lesions are not extensive and do not involve the entire epithelium, and also when the entire epithelium is destroyed over a small area only, the papillary bodies remaining intact. When the destruction extends into the corium, complete regeneration does not take place. This is usually the case in lesions more than one-half centimeter in diameter, the base or stalk of the lesion being one-half or one-third of this. Even in small lesions there is sometimes destruction of the papillæ with inevitable cicatrization. After recovery the papillæ are absent or very imperfectly developed, and the connective tissue beneath has the character of cicatricial tissue.

There are interesting minor modifications of the process due to the character of the epidermis. When the exudation is abundant and further distension of the vesicle or pustule is prevented by the interlacing and connected reticulum, the internal tension may be considerable. Usually the reticulum is ruptured, allowing of further distension. It may happen that space for the exudation is given by its passage through the stratum lucidum and the elevation of the horny layer in mass (Fig. 23). In this way a secondary vesicle may be formed on the surface of the true lesion. In still other cases the entire epithelium with the lesion may be elevated, forming a secondary vesicle beneath instead of above the lesion.

Umbilication of the lesion is usually present except on the palms and soles. It does not appear to be due to the operation of any single cause, but most often to the primary hyaline fibrinous degeneration of the epithelial cells at

the central and primary point of the lesion, which does not allow distension to take place at this point. It is also unquestionably caused by the greater adherence of the cells where sweat glands and hair ducts pass through the epidermis. Serial sections of the vesicle will very often show such a cause for the umbilication. On the other hand, similar conditions should operate to produce umbilication in the varicella vesicle, but this rarely takes place.

Fig. 23.

Two small confluent pustules with separation of the horny layer.

In addition to the large bullæ which are formed usually in the vicinity of the lesions and more or less connected with them, small vesicles no larger than the true lesions and due to the uplifting of the entire epidermis may be encountered. They are rare, but were well marked in one of the cases examined in the Boston epidemic.

The Mucous Membranes.—Eppinger was the first to call attention to the frequency and gravity of the lesions in the mucous membranes; their presence was known to the early investigators. The specific lesions in the mucous membranes show a general resemblance to those of the skin, although there are modifications due to the differences in the tissues. The epithelial cells are in much looser connection with each other, the tissue is more easily permeated by the exudation, and the horny layer is absent. The specific character of the lesion is apparent only in a very early stage. The epithelial cells which are first affected, together with the cells adjacent to them, are thrown off by the exudate, leaving an area bare of epithelium. This takes place more quickly on surfaces covered with cylindrical than on those covered with squamous epithelium. The lesions develop in the same way as in the skin—by the infection and degeneration of circumscribed foci of epithelial cells followed by exudation. The hyaline fibrinoid degeneration takes place as in the skin. In addition to the specific lesions in which the parasites of the disease are found, there are more serious lesions which are non-specific, and at autopsy most frequently found in the soft palate and uvula. They consist chiefly in superficial loss of substance with deep necrosis of the underlying tissue. In these places masses of streptococci are found. It is possible that these lesions are preceded by specific lesions which form the atrium for the streptococcus invasion. Numbers of polynuclear leukocytes are found in these lesions in contrast to the specific lesions. Vesicles produced by the uplifting of the entire epithelium are rarely found in the

mucous membrane. The specific eruption may be found in the mucous membrane of the mouth and fauces, in the larynx, rarely in the trachea and bronchi, and in the œsophagus not infrequently. Only in 1 out of 54 examinations was a specific lesion with the parasitic inclusions found in the mucous membrane of the stomach. In 2 cases a pustule was found in the penile portion of the urethra. None were found in the vagina nor in the female urethra.

Lungs.—The most common lesion is bronchitis, usually combined with more or less extensive bronchopneumonia. Both the large and small bronchi are affected. In 54 autopsies such lung lesions were found in 43. The foci of bronchitis and bronchopneumonia do not differ from those so commonly found in diphtheria. Lobar pneumonia was found in 2 cases. In 8 of the cases the lung exudate was largely hemorrhagic in character, and in 4 cases of purpuric smallpox, hemorrhages were found both in the lungs and on the pleura without any evidence of pneumonia. Different varieties of pyogenic cocci are constantly found in the foci of bronchitis and bronchopneumonia. The streptococcus is most commonly found and next the pneumococcus. Such organisms may also be found in portions of the lung which appear to be normal.

These lung lesions are found in all stages of the disease from the earliest to the latest. They should be regarded as the most common and most serious complications of smallpox. In many cases they are so extensive as to form a sufficient cause for death without the specific disease. They were not more common in children than in adults, although atelectasis was more common in children.

Liver.—The liver is generally enlarged. The average weight in twelve adults was found to be 2,260 grams. The largest size found was 1,500 grams, in a child aged ten years. It must be remembered that the subjects are otherwise healthy and the weights are naturally higher than would be found at ordinary hospital autopsies. In smallpox, the largest livers are found in the late pustular and crusting stages The only condition to which this increased weight can be ascribed is the very evident swelling of the cells, which are larger and more granular than normal. We are accustomed to regard the liver in typhoid as the type of cloudy swelling, but the increase of weight in typhoid (average 1,893 grams in 64 cases) is slight as compared with the increase in smallpox. The fat of the liver is not increased. In 6 of the 54 cases necroses were found. In 3 this took the form of the ordinary central necrosis of the lobule, and in only 1 case was it extensive. In 3 cases there were not distinct foci of necrosis, but single necrotic cells were found without any relation to the lobule. The very small degree of necrosis was singular in view of other evidences of degeneration and of the constant streptococcus infection with which liver necrosis is so often associated in other diseases. Large basophilic cells are frequently found in the capillaries.

Spleen.—This is commonly enlarged in the late pustular stages. The enlargement may be up to 550 grams. The spleen differs in smallpox from that of the other acute infectious diseases in the great diminution in number or the absence of polynuclear leukocytes. In the hemorrhagic forms, and in the early period of the ordinary types up to the completion of the pustular stage it contains in some cases no recognizable polynuclear leukocytes. In the period of desquamation polynuclear leukocytes are fairly abundant. Degenerating leukocytes and nuclear detritus resulting from their necrosis are

found in the purpuric cases and in the early vesicular stages. In the spleen, as in the lymph nodes and in the marrow, the formation of large basophilic cells is a prominent feature. It is particularly striking in the spleens of children in the early pustular stage. These cells are found both in the pulp and in the follicles. Nuclear figures are numerous in the basophilic cells in both places. Enlargement and proliferation of the endothelial cells in the sinuses leading to the formation of large phagocytic cells are also seen, and these often contain cell inclusions. Distinct nodules in the follicles, composed of phagocytic cells and detritus, and similar to the nodules seen in diphtheria, may be found. In addition to these purely cellular changes there is always a varying and in some cases a high degree of congestion.

The lymph nodes are swollen in the beginning of the disease; the swelling persists or increases during the period of eruption, and slowly diminishes. The most common condition is a general œdema producing dilatation of the sinuses and separation of the cells of the follicles. The enlargement of the nodes is due more to this œdema than to cellular hyperplasia. Numbers of large basophilic cells are found both in the sinuses and in the follicles. In many of these cells the cytoplasm around the nucleus is acidophilic, while that in the periphery takes a strong basophilic stain. These cells may be so abundant that the separation of the node into sinuses and follicles is lost, and the node represents a loose mass of cells. The germ centres of the follicles are not apparent. Phagocytic cells are always present; they are most numerous in the later stages of the disease, and are confined chiefly to the sinuses. They are formed by the proliferation of the endothelial cells. The cells of the reticulum lining and crossing the sinuses are swollen and increased in number. Cells are found partially detached which are similar to those within the sinuses.

Streptococci are frequently found in the sinuses. In a purpuric case the writer has found all the sinuses of a cervical node blocked up with streptococci. No reaction is found around them. They exert no influence on the number and varieties of the cells found in the nodes, and they stand in no relation to the necrosis, although both the streptococci and necroses are more abundant in early than in late cases.

Bone Marrow.—Chiari in 1893 investigated the marrow in 22 cases embracing all stages of the disease, and found changes in 86 per cent. He described under the name osteomyelitis variolosa, foci of necrosis and hemorrhage associated with the presence of large cells. The more recent studies of the marrow have been in connection with the changes found in the blood. Muir found a general diminution in cells, which was compensated for by vascular dilatation. The polynuclear cells were almost entirely absent, and the neutrophile myelocytes diminished in number, with only a few of them in mitosis, and occasionally degenerated.

In the examination of the marrow, the writer has found, like others, marked reduction and in some cases complete absence of the polynuclear leukocytes. In one case which died during convalescence, the marrow corresponded to that of active leukocytosis. The absence of leukocytes does not seem to be due to their degeneration and destruction *in loco*, for, save in the purpuric cases, degeneration forms and nuclear detritus are not found. Foci of necrosis varying in size from those easily visible to microscopic areas are found as Chiara described. In early cases there is no reaction around the necrotic foci. In cases dying in advanced and crusting stages, collections

of large cells are found in the fat-spaces around the necrosis. Definite myelocytes are not numerous, and the forms of these with incurved nucleus, the immediate predecessors to the polynuclear cells, are also rare. The most numerous cells in the marrow are basophilic cells similar to those described in the spleen and lymph nodes. Nuclear figures are numerous in these cells, many of which approach very closely to the character of plasma cells, and occasionally it is possible to distinguish in them a small crescent at one side of the nucleus in which the cytoplasm takes more of the eosin stain. Cells of a typical lymphoid character are found in varying numbers, and are more abundant in children than in adults.

Eosinophile cells are less numerous than in the hyperplastic marrow of other infections. Those found correspond chiefly to the eosinophile myelocyte; those with nuclei of the polynuclear type are as generally absent as are the polynuclear neutrophiles.

The large cells first described by Chiari are found in relation to the necrotic foci, and independently of these. They occur both singly and in groups, often surrounding the fat-cells. They are phagocytic for all of the cells of the marrow. They are most numerous in the cases in which there is most hyperplasia in the marrow. Comparison of the marrow of smallpox with that of other infectious diseases has led the writer to regard these groups of large cells as occurring in smallpox alone. They are found in other infections, but not in the same number and grouping. Their chief function seems to be fat absorption. Cells with the same relation to the fat-cells are found in fat-necrosis and in inflammation of the mesentery and omentum.

In cases of purpuric smallpox, hemorrhages of considerable extent may be found in the marrow. Osteomyelitis variolosa is a bad term to apply to the small necrotic foci, as it magnifies their importance. We understand by osteomyelitis an entirely different pathological condition, and one which the writer has never found as a complication of smallpox.

Testicle.—The lesions which are most difficult of interpretation are those of the testicle. There is absence of spermatogenesis save in the cases in which convalescence is established. Normal spermatozoa are absent in the lumina of the tubules, and there is degeneration of the spermatogenic cells. This affects both cytoplasm and nuclei, and the degenerating nucleus assumes forms which present some similarity to certain of the intranuclear parasites in the epithelial cells of the skin. This degeneration is not peculiar to smallpox, but may be found of the same degree and character in typhoid fever. These lesions are absent in undeveloped testicles of children.

In addition to these diffuse degenerative lesions, there are focal lesions as characteristic of the disease as the skin lesions, which are found both in the undeveloped testicles of children and in the adult. The lesions begin as an infiltration of the intertubular tissue with both ordinary lymphoid cells and large mononuclear basophilic cells. The tubules in the foci are unaltered. From such lesions as these, which are best compared with small interstitial foci in the kidneys, the process extends. The area enlarges, the cellular infiltration extends, and finally there is complete necrosis in the centre, with fibrin and hemorrhage in the surrounding interstitial tissue. The necrotic tubules often contain numbers of phagocytic cells. The bloodvessels in the foci are obliterated in some cases by thrombi, but chiefly by the pressure of the cells around them. As in interstitial foci in the kidney, the cells come from the bloodvessels. Nuclear figures are found in those within the

vessels and in the interstitial tissue. Acute endarteritis with accumulations of mononuclear cells is often found.

The lesions vary in number, some testicles showing large numbers of them, while in others they are found only after prolonged search. The smallest lesions, and those best adapted for study, are in the undeveloped testes of children. They show a general relation to the duration of the disease, the most advanced cases occurring late in the course. In 3 of our cases, lesions similar to those in the testicle were found in the epididymis, and in 1 case in the prostate. Brinckerhoff and Tyzzer have found lesions in the seminal vesicle of the monkey in variola inoculata. Cytorytes were present in the epithelium involved in these lesions. Notwithstanding their apparently specific nature, no parasites were found in the testicular lesions of man. Beginning lesions are found in the purpuric cases.

Kidney.—Unrah, in 1872 first called attention to hemorrhage in the pelvis, finding it in 28 of 212 cases. The writer found it in 5 of 54 cases. The epithelial surface is intact, the hemorrhage taking place in and beneath the mucous membrane. It is found in cases in which there are hemorrhages in other organs. It has no connection with hemorrhagic nephritis, this being a rare complication of the disease. The hemorrhage is confined to the mucous membrane of the pelvis and does not extend into the ureters and bladder. In cases of hæmaturia this pelvic hemorrhage seems the most probable source of the blood.

The kidneys are affected in all cases; the most common change is acute degeneration of the epithelium, which occurs in all stages of the disease and at all ages. The kidneys are usually enlarged, rather œdematous, and opaque on section. The degeneration does not differ from that found in other infectious diseases except in being more marked. In 5 cases out of 54, acute glomerulonephritis was found, and in one of these it developed during convalescence.

Small groups of cells are frequently found in the interstitial tissue in various places but chiefly in the upper portion of the pyramid, in the cortex bordering on this, and around the glomeruli. The cell groups are usually quite small, but they may cover a considerable area. They lie both inside and outside the capillaries, which are distended. They comprise ordinary lymphoid cells and large mononuclear basophile cells. Similar cells may be found in considerable numbers in the vessels of the pyramids without any interstitial foci around them.

The writer inclines to believe that the source of these interstitial cell foci is to be sought not in the kidney but in the blood. No condition of the tissue can be found which explains their presence. Similar cells are present in the blood and for some reason tend to accumulate in the vessels of the kidney, particularly in those of the pyramids. The number of cells in the vessels shows that they continually accumulate, for the circulating blood does not contain them in such proportions. The cells lie at random in the vessels and there is no tendency to mural arrangement.

Heart.—Cardiac lesions are infrequent. The writer found acute vegetative endocarditis in 1, an adult who died on the ninth day. There is no enlargement of the heart save in patients in whom there is nephritis. Fat is not infrequently found in the muscle fibers. In 3 cases, 2 of them purpuric smallpox, small but well-marked foci of degeneration were found in the muscle close beneath the endocardium. In 2 cases, both in the late pustular

stage, diffuse areas of necrosis of muscle fibers were found, in one accompanied by hemorrhage and emboli of streptococci.

Inoculation.—There is one form which was formerly of great importance, but which recently has received scant attention and its leading characteristics have been overlooked. This is the inoculated smallpox (variola inoculata) produced by the direct inoculation of the vesicle or pustule contents from man to man. Various means of doing this have been used, the most usual being to make a scratch on the skin into which the inoculated material was placed. When this was practiced, it was regarded as important that the incision should not extend deeply into the corium. The disease so produced differed in marked degree from true smallpox. These differences were always the same and were not due to accidental causes. The period of incubation was eight days instead of ten to twelve, and the disease produced was incomparably milder.

Gregory (1843), who regarded smallpox inoculation as under certain circumstances a valuable method of prophylaxis, has given a good description of the course of the disease. Inoculation is performed by introducing into the arm at the insertion of the deltoid, a minute portion of variolous matter by means of a lancet. The thin lymph of a fifth-day vesicle is to be preferred to the purulent matter of the eighth day, but both are efficient. One incision only is to be made. A minute orange-colored spot is perceptible, by the aid of the lens, on the second day. On the third or fourth day a sensation of pricking is experienced. The punctured point is hard, and a minute vesicle whose centre is depressed may be observed surmounting an inflamed base. On the fifth day the vesicle is well developed and the areola appears. On the sixth day the patient feels stiffness, with pain in the axilla. The inoculated part has become a hard and tender phlegmon. The subjacent cellular membrane has become involved in the inflammatory action. On the evening of the seventh or early on the eighth day, rigors, headache, syncope, vomiting, offensive breath, alternate heat and chill, langour, lassitude, or, in a child, an epileptic paroxysm, announce the setting in of fever. On the appearance of the febrile symptoms, the inflammation of the arm rapidly subsides, and an areola of irregular shape is soon completed, which displays within it minute confluent vesicles. On the tenth day the arm is hard, tense, shining, and very red. The pustule discharges copiously, and ulceration has evidently penetrated the whole depth of the corium. On the eighth day spots of variolous eruption show themselves in various and often in the most distant parts of the body. In a large proportion, the eruption is distinct and moderate, 200 vesicles being considered a full crop. Sometimes not more than 2 or 3 papules can be discovered, which perhaps shrivel and dry up; at other times the eruption is full and semiconfluent, passing through all the stages with as much perfection as the normal disease. With ordinary precautions in the choice and preparation of subjects not more than 1 in 500 cases will terminate unfavorably.

Inoculation was introduced into England by Lady Mary Wortley Montague, whose husband was at the time ambassador in Constantinople. The letter she wrote to her friend, Miss Sarah Chiswell, in 1717, contains the first mention of it. This letter is so frequently referred to and so rarely printed that it is given in full:

"Apropos of distempers, I am going to tell you a thing that will make you wish yourself here. The smallpox, so fatal and so general amongst us, is

here entirely harmless by the invention of engrafting, which is the term they give it. There is a set of old women who make it their business to perform the operation, every autumn in the month of September, when the great heat is abated. People send to each other to know if any of their family has a mind to have the smallpox: they make parties for this purpose, and when they are met (commonly fifteen or sixteen together) the old woman comes in with a nutshell of the best sort of smallpox, and asks what vein you please to have opened. She immediately rips open that you offer to her with a large needle (which gives no more pain than a common scratch), and puts into the vein as much matter as can lie upon the head of her needle, and after that binds up the little wound with a hollow bit of shell, and in this manner opens four or five veins.[1] The Grecians have commonly the superstition of opening one in the middle of the forehead, one in each arm, and one on the breast, to mark the sign of the cross; but this has a very ill effect, all of these wounds leaving little scars, and is not done by those that are not superstitious, who choose to have them in the legs, or on that part of the arm that is concealed. The children or young patients play together all the rest of the day, and are in perfect health to the eighth. Then the fever begins to seize them, and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty on their faces [*sic*], which never mark and in eight days' time they are as well as before their illness. Where they are wounded there remain running sores during the distemper, which I do not doubt is a great relief to it. Every year thousands undergo this operation, and the French Ambassador says, pleasantly, that they take the smallpox here by way of diversion, as they take the waters in other countries. There is no example of anyone that has died of it, and you may believe that I am well satisfied of the safety of this experiment, since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England, and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind. But that distemper is too beneficial to them, not to expose to all their resentment the hardy wight that should undertake to put an end to it. Perhaps if I live to return, I may, however, have courage to war upon them. Upon this occasion admire the heroism in the heart of Your friend," etc.

Her fears of the reception which "engrafting" would encounter at the hands of the medical fraternity were well founded. The clamors raised against the practice, and of course against her, were beyond belief. The faculty rose in arms to a man foretelling failure; the clergy descanted from their pulpits on the impiety of thus seeking to take events out of the hands of Providence; the common people were taught to hoot at her as an unnatural mother who had risked the lives of her children. There is an interesting history of an extensive use of inoculation carried out by her grandson, William Stuart. While he was vicar of Luton, in Bedfordshire, a malignant smallpox epidemic broke out in that neighborhood. The minds of the country people were so distracted with terror that he, having absolute confidence in the practice, offered to have every person, who was still

[1] It is perfectly evident that Lady Mary does not mean to say that veins were actually opened and the virus placed in them, but that the skin was merely scratched.

uninfected, inoculated at his own expense. He had only a country practitioner and country nurses to depend upon, and above two thousand persons were inoculated. Only three people died; an infirm unhealthy woman, a man past eighty years of age, and an infant whose mother afterward confessed she knew it had already caught the disease, which, in her ignorance, she supposed inoculation was to cure. For several succeeding years the smallpox scarcely reappeared in that district.

The only recent reference to inoculation which the writer has found is by Plehn, who describes the process as practiced now in central Africa. The upper arm is used as the site of inoculation, and the contents of fresh pustules are introduced into incisions made with a sharp knife. The result is never a general infection with smallpox but the formation of typical vaccine pustules which in no way can be distinguished from those produced by vaccination. In many cases a group of pustules formed around the site of inoculation, or scattered pustules over the entire body. He never saw a serious illness nor a fatal case.

Notwithstanding the mildness of the disease so produced, there is no diminution in the virulence of the virus which is produced in the lesions. A case of variola inoculata is just as able to transmit the disease in its most virulent form as is a case of variola vera. It was this which led to the prohibition of the practice in England. Circumstances may arise even now under which inoculation may be necessary, as when in the absence of any means for vaccination the exposure of unvaccinated individuals to the disease is inevitable.

Experimental Smallpox.—But little has been done in the experimental study of smallpox. Zulzer, in 1874, was the first to inoculate monkeys, and showed that they were susceptible to the disease and that an exanthem developed. There are reports to the effect that the disease may occur under natural conditions but these are not well attested. Andrew Anderson, in his book on fevers, gives an excerpt from a letter that he received from a friend who was traveling in Central America:

"In the year 1841 I was in the province of Veragua, in New Grenada, to the north of the Isthmus of Panama, and left the town of St. Jago, on the western coast, for David, in Cheriqui, a town in the interior, about 60 or 70 miles to the northwest (and leeward of St. Jago). The smallpox was raging with great violence in St. Jago, but there was no appearance of it in David. A few days after my arrival there, taking my customary morning's ride in the forest, which teems with animal life, I was struck by observing one or two sick and apparently dying monkeys on the ground under the trees. The next morning I was struck by the same singular appearance (for it is very unusual to find a wild animal sick—they instinctively hide themselves), and by thinking that I perceived several on the trees moping and moving about in a sickly manner, I consequently dismounted and carefully examined two, which were on the ground—one dead, the other apparently dying; and after careful examination no doubt remained in my mind that they were suffering and had died from smallpox. They presented every evidence of the disease; the pustules were perfectly formed, and in one instance (that of the dying one) the animal was nearly quite blind from the effects. A few days afterward (I think about four or five days) the first case of smallpox appeared among the inhabitants of David, and in the course of a fortnight one-half of the inhabitants was stricken."

The most extensive experimental study of smallpox was made by Brinckerhoff and Tyzzer, in the Philippine Islands. They found that vaccinia in the monkey runs a course comparable to that in man, that no exanthem is developed, and that only the cytoplasmic forms of cytoryctes occur in the epithelial cells. The result of their study of variola inoculation shows that after skin inoculations, a local lesion which reaches its acme on the seventh day develops, and this is followed by an exanthem which in the majority appears on the eighth day after inoculation and has a duration of five days, the first two of which are employed in growth and the last two in healing. The regional lymph nodes show an enlargement on the fourth and are markedly enlarged on the fifth day. The constitutional reaction occurs at about the height of the active phase of the primary lesion; that is, on the sixth and seventh day of the disease. The temperature reaction begins on the sixth day and persists for two or three days. The decline of the fever is by lysis. The extent of the exanthem varies greatly. In some animals only one typical lesion was present, while in others over a hundred were found. As in man, the exanthem shows a partiality for certain regions. The face was most often the site of eruption. The exanthem presents the same histological features as in man. The parasities are present in the same forms, but the nuclear inclusions, though constantly present, are much fewer in number than they are in man. It was hoped that by the use of the anthropoid apes a disease more closely akin to the natural disease might be produced, but the inoculations of the orang-utan gave results similar to those obtained on Macacas cynomologus, with the exception that the nuclear forms of parasites were more numerous. Inoculations were made in the mucous membrane of the nose, mouth, and palate of the monkey, but were not so successful as in the skin. The constitutional reaction was less marked and a general exanthem developed in only 2 out of 19 animals used. As it seemed evident that the disease produced experimentally corresponded rather with variola inoculata in man than with variola vera, numerous attempts were made to produce the true disease. Both Macacas cynomologus and the orang-utan were in every way exposed to infection, but to no purpose. Thinking that the mode of natural infection was by the respiratory passages, smallpox virus in various forms was blown into the lungs, with the result that a lesion was produced in the lungs which was followed by an exanthem which was more abundant than in the case of skin inoculation, but which occurred at the same time after the inoculation. The virus was also injected into the blood in a single instance without changing either the period of incubation or the character of the eruption, though it was more abundant.

It is evident from these experiments: (1) That the monkey alone of all animals experimented upon is susceptible to smallpox. (2) The form of disease produced by inoculation is allied to, if not identical with, variola inoculata in man. The period of incubation of six or seven days is shorter than in true smallpox; the initial stage (two days) is shorter, and the eruption is less abundant. (3) The monkey is not susceptible to that form of infection which in man produces variola vera. (4) The inoculated smallpox in the monkey confers immunity to both vaccinia and to smallpox.

With our present knowledge of smallpox it is not possible to advance a theory of the disease which conforms to what appears to be known and which is explanatory. Of the mode of infection we are ignorant. The

hypothesis which seems most plausible and which is most generally held is that infection takes place by the reception of the air-borne virus on the respiratory mucous membrane. The organism increases in the favorable soil and produces a local lesion—the so-called protopustule from which the infection of the blood takes place. Blood infection is marked by a sharp onset, and the skin eruption is embolic in character.

There are objections to this view. In the 54 autopsies made in the Boston epidemic a most careful search was made for a lesion which could be interpreted as such a protopustule and it was not found. The period of incubation which should correspond to its development is without symptoms. It is possible that it might have been present and healed without producing symptoms or perceptible remains of a lesion. Lesions of tuberculosis considerable in extent may be present in the lungs without producing symptoms. If we can judge by the character of the protopustule which is produced by the inoculation of the skin, such a lesion in the lung would have produced symptoms. The lung tissue does not seem to be a favorable soil for the development of specific lesions. They are but rarely found in the bronchi and not at all in the lungs. In support of the protopustule idea, cases have been known in which accidental infection of the skin and mucous membrane has been followed by an eruption. But these seem rather to have been cases of variola inoculata than of variola vera. Variola inoculata is produced in monkeys by blowing the virus into the lungs. It is known that the Chinese inoculated for the disease by placing crusts from the eruption into the nostrils, but whether the disease produced was vera or inoculata is not known.

Any theory of the disease must take into account the three forms. From the contents of a smallpox pustule in man there can be produced vaccinia in the rabbit and calf, variola inoculata in man and in the monkey by skin inoculation, and probably variola vera in man by infection in an unknown manner. We cannot explain variola inoculata by the site of inoculation. We know that in other diseases the course of the disease may be modified by the locus of inoculation, one locality offering a more unfavorable soil than another. The disease in the monkey is the same whatever site be chosen, and we do not know that it would be different in man. It is always assumed that the virus is contained in the skin lesions, and there is much evidence for this. They certainly contain virus which will give rise to vaccinia and to variola inoculata, which latter will in an unknown way give rise to variola vera, just as the latter will propogate itself.

We do not know when the general infection of the blood takes place. The general disturbance which the onset shows has been regarded as evidence that blood infection takes place at this time, and the general disturbance may mean that the organisms have at this time been destroyed in the blood and the toxin set free. It is not at all necessary to assume the existence of a protopustule, for in variola vera the entire stage of development may pass in the blood. We know nothing of what takes place during the stage of incubation. It is difficult to explain the eruption otherwise than as due to a deposit of the organisms in the skin by means of the blood. Their development in the skin is not incompatable with the assumption of blood immunity, for there they would be withdrawn from the action of the germicidal factors.

In all of the investigations of the blood, made in Boston, the organisms have not been found in the circulation. It has not been possible, however, to examine the blood in the period of incubation at which time it seems that

the blood infection most likely takes place. In examinations during the initial and eruptive stage, organisms were not found in the blood, nor did the inoculation of the cornea give a positive reaction. It would seem that purpuric smallpox must differ in some way from the general course, but in what the difference consists is unknown. It cannot be a matter simply of diminished resistance of the individual to the organism permitting an enormous increase, for there would then be transitions between the purpuric and the ordinary forms. It would be possible to explain it either by the assumption of absence of a general blood immunity, or of the destruction of the blood complement permitting an unlimited infection by streptococci.

Although bacteria can be excluded as a primary cause of smallpox, they play a prominent part in its pathology. The writer is inclined to regard bacterial infection as more important in bringing about the fatal termination than the specific parasite. It is impossible to say to what extent the lesions in internal organs are due to bacteria and their products. Some of them, notably the changes in the blood and blood-forming organs, and those in the testicle, are probably specific, and due to the action either of the specific parasite or its toxins. The writer has never been able to demonstrate the parasite in the lesions in the testicle, though Brinckerhoff and Tyzzer have found it in lesions of the seminal vesicle produced experimentally in the monkey. The degenerative lesions are very much the same as in other infectious diseases in which there is a combined bacterial infection. There is also evidence of the absence of tissue inhibition to bacterial invasion and growth given in the abundance and character of the growth in the tissues. The bacteria are chiefly streptococci. There is analogy in respect to the importance of the part played by bacteria in the other exanthemata, notably in scarlet fever.

It has been shown that the immunity conferred by smallpox and vaccination is due to a bactericidal or germicidal property acquired by the blood serum (Sternberg and Reed, Beclere, Chambon and Menard). In the comparative study of smallpox and vaccinia in the monkey, the unexpected fact was developed that the immunity produced by vaccinia was stronger than that produced by variola inoculata. The vaccinal immunity protected perfectly against both vaccinia and variola inoculation, while that produced by smallpox inoculation protected from smallpox but only imperfectly from vaccinia. The study of the period of immunity development by daily inoculation and vaccination showed that the immunity produced by variola inoculata appears between the fifth and the eighth days and the exanthem develops in an immune animal. The immunity which is produced by vaccination in the monkey appears between the sixth and the eleventh days.

There are certain questions which present themselves. These relate, first, to the parasite and its life-history; second, to the interrelationship of variola vera, variola inoculata, and vaccinia; third, to the immunity and its mode of production; fourth, to the mode of production of the exanthem; fifth, to the mode of infection in variola vera. There is some positive knowledge on all these points; but there is yet lacking the chain which will so connect them that the disease as a whole becomes clear.

Symptoms.—The period of incubation has been more accurately determined in smallpox, owing to the suddenness of the onset, than in any other infectious disease. It is but rarely that cases suitable for this determination

are found, and they are more apt to be sporadic. The exposure must be but once and for a short time. A sufficient number of such cases have been recorded by competent observers. All are agreed in placing the time between ten and twelve days in the great majority. Welch and Schamberg have seen cases in which it was sixteen days and one in which it was five and one-half days. Knecht reports one case of seven and one-half days.

In general the length of the period of incubation is of no influence in determining the character of the disease. Zuelzer says that in purpura variolosa the period is shorter, being from six to eight days in 9 cases. In the 10 cases of this seen by Bancroft, the period could not be determined. Usually there are no symptoms, the individual being in perfect health and pursuing his occupation until the onset. Curschmann found in 11 out of 1,000 cases, indefinite symptoms such as languor, pain in the head and back, or slight gastric disturbances. The rarity inclines one to believe that when such symptoms are brought out by questions, they are imaginary or have nothing to do with the disease.

The initial stage (the period between onset and the appearance of the eruption) is found in practically all cases, and forms one of the most characteristic features of the disease; it is even more characteristic than the eruption, for this may be absent (variola sine exanthema), or atypical (purpura variolosa). The duration of the initial stage is usually three days. Bancroft found variations from this in 263 out of 530 cases. In 7 the initial stage was absent or the symptoms were so slight as to be unnoticed; in 26 it lasted for one day; in 91, for four days, and in 139, for two days. Analysis of these cases showed no relation between the length of the initial stage and the severity of the disease.

The onset is usually sudden and marked by definite symptoms, such as great depression, headache, backache, chill, and vomiting; occasionally it is gradual and accompanied by malaise, fugitive pains, and gastric disturbances. The severity of the initial symptoms varies, but there is little relation between the initial severity and the character of the disease, since very light cases may begin with stormy initial symptoms. Mild initial symptoms as a rule preclude the more severe forms. The depression may be marked; there is a feeling of weakness and giddiness, with disordered consciousness. It not infrequently happens that individuals found on the streets in this condition are taken up by the police as being drunk, and the true condition becomes apparent only when the eruption appears. The depression is much greater than in typhoid fever, for in the depression of smallpox the patient is unable to stand, or staggers as if drunk. When brought into the hospital, the face appears sunken and pale, the features expressionless, the extremities cold, and the pulse small and frequent. The patient gives the impression of one overwhelmed by a poison. Children frequently show the beginning of the disease by general convulsions. Other disturbances of the central nervous system are seen. Insomnia, in part due to pain, is common even in the mild forms of the disease. Somnolence, sometimes to the extent of coma, is seen, especially in children. Bancroft saw one child in the status epilepticus with constantly recurring convulsions for an entire day. Many patients complain of terrifying dreams, and will even try to keep awake to avoid them. Delirium is common and is usually of the type seen in drunkards. In spite of the delirium the patient may be roused and made to answer questions. Sometimes the most violently delirious will suddenly become

rational. Catatonia and sensory disturbances in the form of local anæsthesia have been described. Bancroft saw disturbances of speech exclusive of those incidental to delirium, in 3 cases,—in 1 consisting of a slight stammering, and in 2 of a transitory aphasia lasting from the first to the fifth days.

Headache as an early symptom is common; it is usually severe and often sharp and agonizing to such a degree that patients make violent outcries and grasp at the head. It usually extends over the entire head, or may be confined to the forehead and temples. It is often described as though a band were encircling the head, or as a lancinating throbbing pain. It may continue unchanged during the entire initial stage and gradually subside as the eruption appears. Backache, usually localized in the lumbar region, is a well-known symptom. This has especial importance in the early diagnosis because it appears in no other acute febrile disease so frequently or with such intensity. Sydenham compares it to the pain of kidney colic. It may be accompanied by pain in the thighs, hips, bones, and joints, or extend over the sides and simulate the pain of pleurisy. Pain and stiffness in the muscles at the back of the neck is not uncommon. The pain may occur with the onset of the disease or in the last days of the initial stage, and usually disappears as the eruption comes out.

Gastric disturbances are common during this stage, at the onset in the form of nausea and vomiting, and later as anorexia and vomiting. The tongue is usually covered with a whitish-yellow coat and bears the marks of the teeth; the breath is offensive. Injection and swelling of the tonsils and pharynx are often seen, and pain is complained of by the patients. In those cases with pharyngitis there is apt to be a more extensive eruption on the mucous membrane than in the cases without this symptom.

Menstruation appears almost regularly in the initial stage, even when the regular period has not arrived, and is usually abundant. This may be of importance in the early diagnosis of the disease. In pregnant women miscarriage is common at this period.

A chill more or less definite in character usually marks the onset. The temperature rises rapidly to about 104° F. and remains at this height with slight morning remissions for about three days. In the lighter cases the temperature falls to normal at the end of the third day; in the more severe, the decline is gradual and the return to normal not completed before the fifth or six day of the disease. With the fall in temperature the eruptions appear, the full development of which is reached after normal temperature is established. In a case of moderate severity the temperature usually reaches the normal point two days after the beginning of the eruption. The pulse and respiration are increased in proportion to the degree of the fever. The urine at this time usually contains albumin and presents the characteristics common to febrile diseases. The spleen is variable, sometimes being enlarged, usually not. The initial illness may be so severe that the patient may die before the appearance of the eruption (variola siderans).

The recognition of the appearance of rashes during the initial stage of smallpox is of comparatively recent date. It seems hardly possible that they could have been overlooked by the earlier observers, and it has been supposed that they did not occur. Sydenham makes no mention of them; but then he did not clearly distinguish purpura variolosa from variola hemorrhagica, although he must have seen both types; nor did he distinguish varicella from variola. The rashes were seen by some observers who

regarded them as due to mixed infection with measles or scarlet fever. The first description of the rash was given by Rembold, in 1840. He says, "Cases are seen which have been regarded as a combination of smallpox with other diseases. I have observed cases of this sort at different times, and hold another view regarding them; namely, that they are not independent exanthemas appearing simultaneously with smallpox, but a condition of the skin which seems to introduce the smallpox eruption." The classical description of the rash is by Simon, in 1870. Its frequency varies greatly in different epidemics, but it is never common. Bancroft observed initial rashes in 16 of the 1,200 cases seen by him. The rash may be erythematous or petechial, and may last from a few hours to several days. The erythematous rash usually appears on the second day of the disease, reaches its full development on the third day, and finally disappears before the development of the specific eruption. The rash varies from a mere flushing of the face to a general erythema in which the entire body is of a bright-red color. It is often faint over the lower extremities, even when intense elsewhere, and it may be mottled, alternating with areas of normal skin. The eruption may be composed of fine macules.

The second and the more common form is the petechial. It may occur alone or associated with the erythema. It may appear as a diffuse, dark-red erythema, which only upon pressure discloses bright-red round or oval petechiæ from 1 to 2 millimeters in diameter. Bancroft found the petechiæ to be numerous in scar tissue, particularly in the lineæ albicantes of the abdomen. The petechial rash lasts longer than the erythema. Its appearance changes rapidly after the third day, when the associated erythema disappears and the petechiæ become yellowish brown and at the end of the week generally disappear. The favorite seat of the petechial eruption is the lower abdominal region, together with the genitals and the inner surfaces of the thighs. With the patient lying on the back with the legs in contact, the affected area takes the form of a triangle, the apex of which is toward the pubes and the base crosses the abdomen transversely in the neighborhood of the umbilicus. It may also extend up the lateral surfaces of the trunk to the axilla, and from this point it frequently invades the axillary folds, the contiguous portions of the arm, and the pectoralis major muscle, forming the brachial triangle of Simon. Curschmann says he has seen in women, a macular initial erythema around the nipples in cases otherwise free. The rashes are as common in men as in women, and have no prognostic importance. The fact that the petechial rash appears on parts of the body which are comparatively little invaded by the pock eruption has led to the idea that they protect the parts from the pocks; but there may be a full development of pocks in the region formerly occupied by the rash. There is another form of rash which develops late in the disease, within or following the period of crust formation. Bancroft observed this in a small number of cases all of which with one exception occurred within a space of three months and near the close of the epidemic. Knecht was the first to call attention to these cases. According to Simon there is usually no increase of fever with the eruption, or it is slight. In most cases there is intense reddening of the fauces and swelling of the tonsils. Some of the cases of this which Bancroft has described depart so from the usual type that it is difficult to avoid the conclusion that they were instances of mixed infection with scarlet fever. Bancroft's cases occurred in the more severe types of

smallpox, usually about the thirteenth day, and the rash was preceded by fever amounting to 104° F., headache, nausea, and vomiting in 7 cases. The eruption commonly appeared either with the rise of temperature or on the day following, and closely resembled scarlet fever. In the more severe cases the erythema was general; in the lighter it was localized on the abdomen, on the flexor surfaces of the arms, on the legs, in the folds of the axilla, and on the groins. Its duration was ordinarily from two to three days, and it was followed by desquamation. In two cases there was an associated suppuration in the region of the elbow. One case which showed a rash on the ninth day of the disease, accompanied by fever on the ninth, twelfth, and fifteenth days, was discharged from the hospital on the twenty-fifth day, with desquamation incomplete. Eight days later a member of his family was admitted to the scarlet fever ward of the Boston City Hospital, with no known source of contagion. On the other hand, Bancroft, who was constantly exposed to cases of this sort, six months later, after the conclusion of the work at the smallpox hospital, contracted scarlet fever.

The end of the initial stage is marked by a decline of temperature, which may reach normal, and a general abatement of all the symptoms. The intellect becomes clear, sleep is restored, the headache and pain in the back cease, and the patient may possess a good appetite and normal digestion. In this we have another peculiar and characteristic feature of this remarkable disease.

Eruption.—The eruption is preceded by a diffuse erythema most marked on the forehead. The eruption varies widely according to the part of the body involved and the thickness of the skin. Patients ordinarily notice it first on the forehead and wrists. Close examination may show a few macules on the abdomen before these regions are affected.

The lesion first appears as a small red macule 1 to 3 millimeters in diameter which in the beginning is slightly indurated. It becomes pale on pressure; on removal of pressure the blood quickly returns. A capillary pulse is often seen in the macule, and most readily immediately after the removal of pressure. Within the middle of the macule there appears a small gray spot which gradually becomes filled with fluid. It increases in size, chiefly at the periphery, so that the periphery rises above the level of the centre, producing a crater or umbilication. It becomes a tense hemispherical elevation, generally umbilicated, though it may be rounded, contains a gray transparent fluid, and is surrouned by a red areola. The pock gradually assumes a yellowish tinge and by the eighth day of the disease it is filled with a distinctly puriform fluid. It is not possible to empty either the vesicle or the beginning pustule by a single puncture. The fluid is contained in a number of cavities within the epidermis, and these do not communicate until a very late stage of pustulation. Close examination of the beginning vesicle, using a magnifying glass in bright light, shows that it is composed of a number of very minute clear points which correspond to the single collections of fluid in the epidermis. From the climax of development shown by the large tense umbilicated pustule, a gradual retrocession, beginning usually on the tenth day, takes place. The lesion becomes less tense, its fluid contents disappear, and it becomes converted into solid reddish-brown material. This for a time is closely adherent, but later separates and falls off as a flat, hard, circular disk of an average diameter of 3 millimeters. In the beginning the macule is usually slightly indurated.

and with the increase of the exudation within the epidermis the induration increases. In both vesicles and pustules the induration is marked; it is distinctly circumscribed, and gives the impression of a shot beneath the fingers.

In the lesions on the face the initial induration is more marked than elsewhere. The early lesion of the face is a papule often with a shallow depression at its apex. The evolution of the lesion is here more rapid than elsewhere, and the pustular stage more quickly reached, the climax of development occurring on the eighth or the ninth day. By the ninth day, in all but the lighter cases, an exudate appears upon the surface of the pock, consisting of a thick yellowish material which soon dries into a gray or greenish-gray crust. When the lesions are close together this may completely envelop the face and harden into a tough brown mark. When the pocks are separated, the exudate in drying forms a disk upon the apex of the pock. Upon the scalp the lesions appear later than they do upon the face and may cause great pain.

Upon the hands the eruption is abundant, and the tension produced by the pocks and the accompanying œdema causes great pain. The pain is intense when the pocks develop beneath the nail. The patient usually assumes a characteristic attitude, elevating both hands and spreading the fingers as widely as possible. When the horny layer of the epidermis of the hands is thick, the pock may pass through all of its phases without distinctly elevating the surface. After the absorption of the fluid of the pustule, large disks remain beneath the horny layer, which must be picked out before the patient is discharged from the hospital. It is a common sight in a smallpox hospital to see convalescing patients relieving the monotony of idleness by picking the disks from the soles and palms of one another.

The eruption on the trunk is later in appearing than on the face or on the arms. It is usually less abundant on the abdomen and in the groins than elsewhere. It is profuse on the back, especially in its upper part, and here the lesions are generally accompanied by an extensive area of erythema surrounding the areola, forming irregular rectangular areas, the long axes of which are parallel with the ribs. This erythema persists until the pustular stage is reached. In general the lower extremities exhibit the eruption later than any other part of the body, although a small area of pock formation may appear very early upon the inner aspect of the thigh. The leg from the ankle to the knee is often almost wholly free from the eruption.

The development of the pock is accompanied by œdema of the corium and subcutaneous tissues. This is most marked on the face and eyelids, often causing complete closure of the eyes,—Sydenham says "the eyelids themselves being no bad representations of an inflated and translucent bladder drawn across the eyes." The swollen countenance covered with brownish-yellow crusts, the closed eyes, the thick protruding lips dribbling saliva, and the uplifted hands, give a terrifying aspect to the patient.

The lesions on the face dry first; next, those on the arms; later, those on the trunk and the lower extremities. In children, owing to the thinness of the epidermis permitting the fluid of the pock to come through, and owing to the greater tendency to injury of the lesion, crust formation is more common than in the adult. The crusts of the individual lesions fall off, and sometimes the epidermis of the palm or the sole is cast off in one

PLATE III

Serial Photographs of Smallpox in an Unvaccinated Man.
Third Day of Eruption. (Welch and Schamberg.)

PLATE IV

Fourth Day of Eruption. (Welch and Schamberg.)

PLATE V

Sixth Day of Eruption. (Welch and Schamberg.)

PLATE VI

Eighth Day of Eruption. (Welch and Schamberg.)

PLATE VII

Tenth Day of Eruption. (Welch and Schamberg.)

PLATE VIII

Twelfth Day of Eruption. (Welch and Schamberg.)

PLATE IX

Sixteenth Day of Eruption. (Welch and Schamberg.)

PLATE X

After Recovery. Scarring Present, but Not Deep.
(Welch and Schamberg.)

piece, carrying the disks upon its inner surface. Scars result when the lesions are sufficiently deep to destroy the papillæ. The extent and character of the cicatrix depends upon the depth of the lesion. In studying the healing lesions in every stage the writer never found any regeneration of the papillæ. In severe cases the nails fall off, and in nearly all cases the hair is lost during convalescence.

The eruption on the mucous membranes is typified by that on the soft palate. It begins here, often before the appearance of any lesions upon the skin, with the formation of a papule. The papule develops into a vesicle which ruptures, forming a deep white erosion. The rupture takes place so early that in but one or two instances has the writer been able to find unruptured lesions at autopsy. The eruption is most abundant upon the soft palate, although the entire mucous membrane of the fauces may be affected.

The pocks may develop atypically. One of the most common variations seen in severe cases is delay in the evolution of the eruption, whereby the pocks, which in lighter cases are well filled out and pustular by the eighth day, do not reach their full development before the twelfth day. Another atypical condition is seen occasionally toward the fatal termination of the disease. Instead of developing into full, rounded pustules, the pocks may remain umbilicated, or even flatten down, puckering in the centre, and presenting a dull gray instead of a yellow color.

Not infrequently, and in cases which do not belong to the hemorrhagic type, the centre of the pock becomes dark-red from hemorrhage. This condition is seen most frequently in the lesions of the forearms and legs. In certain cases the development of small vesicles is seen, which have nothing to do with the pock formation but are due to the elevation of the entire epidermis by the œdematous fluid coming through. They vary in size from small foci, no larger than the beginning small pock vesicle, to large bullæ. They may be filled with clear fluid or the fluid may be dark from admixture with blood. The bullæ may occur in the midst of pustules, in which case these are elevated or split horizontally. Similar vesicles may be seen in the mucous membranes.

Any condition which gives rise to any irritation of the skin influences the eruption, probably by causing increased vascularity. The eruption is often peculiarly abundant on the neck, where the collar is worn; along the line of pressure at the waist; and, in women, where the garter is worn. In a musician there was an abundant eruption on the shoulder where the body of the violin rested. There have been many observations of an abundant eruption in areas of hyperæmia produced by a mustard plaster or iodine. An area of abrasion of the skin produced during the stage of incubation was surrounded by groups of pustules. On the other hand, one patient came into the hospital with an antiseptic dressing around the foot and lower leg which was allowed to remain. There was a very abundant eruption elsewhere on the body and a total absence of eruption in the area beneath the bandage.

According to the character of the eruption, smallpox has been divided into a number of varieties. It must be remembered that such a division is artificial and the varieties merge into one another by intermediate forms. The typical cases of each variety are, however, fairly distinctive.

Variola Without Eruption.—This is the febris variolosa of Sydenham. In the epidemic in Boston cases of this were seen. It appears as illness of an indefinite character, occurring chiefly in hospital attendants on the twelfth

day after exposure to smallpox. The symptoms consist in headache, pain in the back, fever, and nausea. They may be so slight that the individual pursues his ordinary vocations, or they may approach in severity an ordinary initial stage. The symptoms last two or three days and then suddenly abate. The condition was well marked in one of the physicians investigating the disease during the Boston epidemic in 1901. Characteristic initial rashes may appear during the attack. One patient, a pregnant women, remembered having a headache about two weeks after exposure to the disease, but was not otherwise affected. Her child showed a typical eruption when two days old. A group of 3 cases which appeared in one of the large hospitals in Boston, the onset in whom was nearly simultaneous, was traced to a ward tender who had an attack of what was supposed to be the "grip." As the disease is capable of being transmitted during the initial period and before the eruption, the importance of the recognition and the isolation of such cases during an epidemic is obvious.

Mild Smallpox.—The term varioloid (resembling smallpox) should be excluded from the nomenclature of the disease. The initial period in this may be typical and severe or mild. The symptoms suddenly abate, and are followed by an eruption which may consist only of a few pocks. Welch and Schamberg report a case in which but a single pock appeared. The pocks are usually small and superficial, and may easily be overlooked or their nature unsuspected. Inquiry at the time of removal to the hospital of a patient with well-marked smallpox, often brought to light the fact that about two weeks previously another member of the household had been sick, who, upon examination, showed a few healed pocks. In one such case the crust of the "pimple" from a suspected individual gave the characteristic corneal reaction in the rabbit. In these slight eruptions the pocks are apt to be most abundant on that part of the body most subject to the eruption in the well-marked disease. Some pocks are usually found on the forehead. They may heal without leaving a perceptible scar. Usually an individual with a slight eruption of this sort is able to follow his occupation. Unless the pocks are fairly numerous on the face, the disease will be entirely overlooked. There is no doubt that the disease is frequently spread by these mild cases. The habit of calling such cases varioloid has done much evil. The character of the disease is not at all influenced by the character of the attack from which the infection is derived. Cases of confluent and purpuric smallpox are just as apt to follow infection by these mild cases as from any other form.

In the pandemic of 1901–02 in certain parts of the West and South, most of the cases were of this mild variety. The writer had the opportunity of examining the lesions removed during life from a number of these. Histologically they presented no difference from the same stages of lesions in the severe cases. Both the protoplasmic and the intranuclear forms of the cytorcytes were present in the same numbers and relations. Such cases are now rarely found except in vaccinated individuals. They may occur in unvaccinated individuals, as is evident from the descriptions of the disease in the prevaccination period and in epidemics which take a very mild course. The mild cases are certainly very much more prevalent toward the close of an epidemic than at any other time.

Abortive Smallpox.—There is properly a distinction between this and the mild, but it is often used to designate the same condition. It includes

PLATE XI

Smallpox. Skin of the Soles of the Feet Cast off in One Piece and Showing Disks.

those cases in which the lesions are numerous in the beginning, appear to be following the usual course, and suddenly abate. The initial stage may be mild, or of the most severe type, accompanied by delirium and unconsciousness, and continue for four or five days. The lesions may be smaller and more superficial than usual. The vesicle develops on the apex of the papule, never completely replacing it, and on the fifth and sixth days, instead of becoming a full, tense pustule, collapses and dries up, forming a thin brown crust which is soon desquamated. Such cases of abortive smallpox have an interest in that they have been confounded with varicella and have led Hebra and others to deny the duality of the two diseases. This modification of the ordinary eruption is seldom manifested by all the pocks upon the body; more commonly certain lesions continue to develop into fully formed pustules, so that scattered among the abortive pocks are occasional typical pustules. The lesions of the lower extremities show the least tendency to modification.

Discrete Smallpox.—This is the ordinary form, and includes all those cases in which the lesions are not sufficiently numerous as to be confluent. Attacks in which the lesions are everywhere discrete usually follow a mild course. In 54 autopsies no cases with well-developed pustules were found in which there was not some confluence. The cases without confluence were those which died in an early stage of the disease before the eruption was fully developed, or those in whom the eruption followed an atypical course.

Confluent Smallpox.—In this the eruption is so abundant that the lesions do not develop independently but in the course of their formation merge into one another. Pustules may be very closely set and be seemingly confluent when they are not really so, the single lesions being separated by short intervals. Confluence takes place during the early active period of the development. From the histological study of the lesions it is evident that the development does not take place diffusely over a large area of the skin, but from single foci which in the course of their development coalesce with those immediately adjoining. The confluence takes place in those parts where the eruption is usually the most abundant, most frequently on the face. The confluence may be apparent at the end of the first week of the disease. The confluence is seen, next to the face, most frequently in the eruption on the ankles, on the dorsum of the foot, on the hands, and on the arms. In very severe eruptions the lesions may be confluent almost everywhere save on the trunk. The confluence undoubtedly signifies a more severe type of the disease. There is nothing in the confluence *per se*, it merely denoting a more abundant eruption and complete development. Sydenham calls attention to the importance which the abundance of the eruption on the face plays in denoting the severity of the case. It is rare to find a case of typical confluent smallpox in an individual who has been vaccinated. In the old epidemics it often happened that the majority of the cases followed this type.

Hemorrhagic Pustular Smallpox.—A tendency to hemorrhage in, and in the vicinity of, the pocks always denotes a grave form of the disease. The eruption in these cases is abundant, but fully developed pustules are not numerous. The contents of the pocks may be hemorrhagic, but the tendency to hemorrhage is best marked by the presence of petechiæ in the skin around them. Such petechiæ are seen chiefly on the face, legs, and

arms. In one of our cases they were so closely set on the legs as to give the skin a deep-purple color. Small vesicles may be seen on the surface of the petechiæ. Bullæ with hemorrhagic contents are also found. Sydenham described these and recognized their importance in prognosis. He describes them appearing upon "a ground covered with innumerable pustules, conspicuous in size and filled with a clear serum. When the vesicles were broken the skin underneath was black, and, as it were, mortified. Death was the lot of all those whom I ever saw with this fatal symptom." Such hemorrhagic cases seem to occur by preference in drunkards and in individuals weakened by some antecedent disease. The tendency to hemorrhage is not confined to the skin, but there may be hemorrhages in the mucous membranes. Hæmaturia in both this and purpuric smallpox may result from hemorrhage in the pelvis of the kidney.

Purpuric Smallpox.—This is the most atypical and fatal form of the disease. It is doubtful if a well-marked case ever recovers. It is doubtful if a sporadic case would be correctly diagnosed, particularly if the physician were unacquainted with smallpox. It departs so much from the ordinary type that its status as a definite form of smallpox was not established until the German epidemic of 1870. It is evident that Sydenham did not recognize it. The disease is most apt to be found in the midst of an epidemic, but can also appear sporadically. The frequency varies. In the epidemic of 1901–02 Bancroft found 12 cases in 1,200. It is generally held that it occurs most frequently in young and robust individuals, in men more often than in women, and that it is as apt to appear in individuals who have been vaccinated as in those who have not. In Bancroft's 12 cases recent vaccination had not been practiced in any, although unsuccessful attempts had been made in 2 within the two weeks preceding the onset of the disease; primary vaccination in childhood had been attempted in 7, of which only 3, men of an average age of twenty-seven years, showed typical foveated scars; 3 were unvaccinated. Ten of the cases were men and 2 were women; neither of the women was pregnant. The average age was thirty-four years. The onset is usually stormy, with chill, nausea, vomiting, and intense headache. This is not necessarily the case; 2 of Bancroft's patients worked during the first two days of the initial stage. The fever at onset is as a rule not so high as in ordinary cases. Usually on the second day a superficial bright-red erythema resembling that of the initial rash appears, first on the chest, arms, and face. Within twenty-four hours this may spread over nearly the entire body, and is accompanied by marked increase in the constitutional disturbances. Severe deep-seated and agonizing pain is felt in many parts of the body, including the bones and joints, but is most intense in the precordium and epigastrium. The erythema changes from a bright-red to a dark terra-cotta color. Petechial ecchymoses appear in it and may present little contrast with the general dark color. In extreme cases the entire body takes a general dark plum color on which the petechiæ and ecchymoses may be faintly seen. There is great œdema, especially of the face. In the mucous membranes the same tendency to hemorrhage is seen. There is bleeding from the nose, and the nostrils may be partly occluded by the crusts of dried blood. Bloody saliva, due to hemorrhage from the gums, trickles from the mouth; there is a cough with bloody expectoration. The tongue, though swollen and coated, does not show the same tendency to hemorrhage as the other mucous surfaces. Women have abundant metrorrhagia, and abort if they are pregnant.

The urine is scanty, high-colored, albuminous, bloody and contains blood-casts. The pulse is high and proportionate to the fever. In many cases death takes place before the development of any eruption. In some cases a few superficial vesicles on the face or elsewhere may be seen. In one of the most typical cases, the only evidence of the eruption was a few scattered vesicles around the ankles. Individuals who live until the fifth or sixth day of the disease may show the beginning of a typical eruption. The sensorium is clear even toward the last; patients may be drowsy but they can be easily roused and answer questions intelligently.

The relation of this form of purpura to smallpox is now no longer in doubt. It occurs only after exposure to the disease, and exposure to it may be followed by the typical disease. All doubt is easily set aside by the histological examination of the skin. This shows everywhere the earliest lesions preceding the formation of macroscopic vesicles. The foci are so numerous that had the disease progressed the entire body would have been covered by a confluent pock. In all of the cases examined by the writer, there was an intense streptococcus septicæmia. There is no tendency for the disease to propagate itself; it may arise from and give rise to the mildest forms of smallpox. Death takes place at an average of between four and five days from the onset. It is rare that life is extended beyond the sixth day.

The temperature curve in a case of discrete smallpox is almost as characteristic as the eruption. There is a sharp rise of temperature at the onset, which is maintained with slight irregularities during the entire initial stage. It then falls, in some cases rapidly, in others by degrees, to the normal or a little above and maintains this during the vesicular stage of the eruption. At the beginning of the stage of suppuration, at the end of the first week of disease, there is another rise, not so sudden as at the onset, nor does it ordinarily reach the same degree. The temperature is maintained through the stage of suppuration until the beginning of desiccation, when it again falls, in some cases rapidly, in others by degrees. There is much more irregularity in the second rise than in the onset. Fig. 24 shows a curve from an ordinary rather mild case of discrete smallpox.

FIG 24.

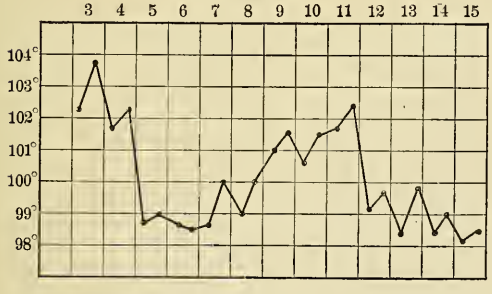
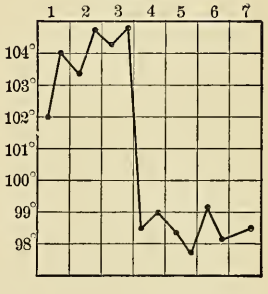


FIG. 25.

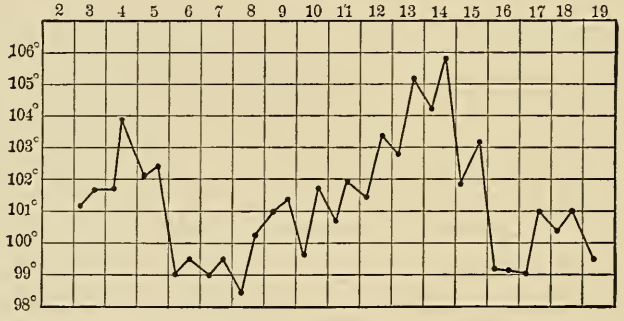


There has been considerable discussion in regard to the pathology of the fever. Pfeiffer regards the first rise as specific and denoting the primary infection of the blood with the organisms which have entered from the hypothetical protopustule. At this time the organisms are deposited in the skin, where a second crop of organisms is produced, which again enter the blood and give rise to the secondary fever. There is not much in favor of

this view. The onset of smallpox denotes the sudden action of a toxin. Not only the fever but the whole train of phenomena, especially those in the nervous system, seem capable of explanation by this view only. The writer is inclined to regard the primary fever as denoting not blood infection but immunity. At this time the organisms in the blood are destroyed and the toxin combined with them is set free. Those organisms responsible for the skin eruption have been brought to the skin before. This view is in harmony with experimental evidence, as to the time of immunity production and the infectiousness of the blood. No experimental study of the blood has been made during the stage of incubation. The blood is not infectious so far as can be determined experimentally during or after the initial stage. There is no warrant for the belief that the second rise is anything more than the fever of suppuration and due to absorption from the skin. Its curve is in no way specific, and the fever varies in degree with the severity of the pustulation. The secondary fever does not necessarily take place. Fig. 25 is from a case of mild smallpox with high initial fever and sudden fall. The low temperature was maintained during the course of the slight eruption.

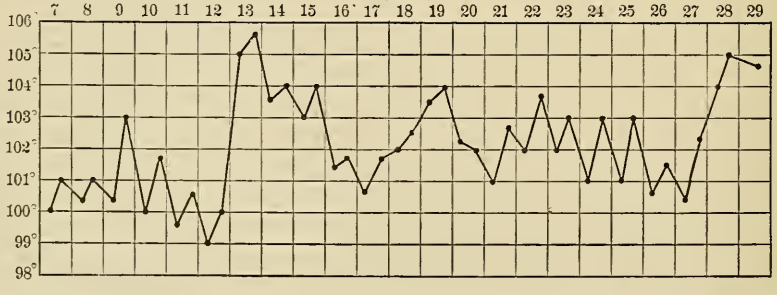
While the fall of the secondary fever is generally by lysis, there may be a sudden fall as in the primary fever. Fig. 26 shows a case in which the high

Fig. 26.



secondary fever fell suddenly in two days from a height of 106° to the normal. Fig. 27 shows a curve from a case in which there was a third rise coincident

Fig. 27.



with the appearance of the secondary scarlatiniform rash and which terminated fatally on the twenty-ninth day of the disease. The secondary fever, being due to the suppuration in the skin and the absorption of the products from this, will be influenced by the varying conditions of the suppuration.

Both the degree and the duration of the secondary fever is in proportion to the severity of the skin lesions. In slight cases it may not last more than three to six days, while in severe confluent cases it may last six to twelve days and may merge into the fever due to complications. In cases terminating fatally there is often a high rise of temperature preceding death. Simon found temperatures of 110° and 112° F. immediately after death. In purpuric smallpox, the temperature neither in the onset nor in the course of the disease reaches the height observed in ordinary cases.

Not only the fever but also the other phenomena of the suppurative stage denote toxic absorption. Delirium is common, not only in alcoholics, in whom the most violent forms are seen, but in other patients. This is also in great part dependent upon the severity of the eruption. Patients in delirium often strive to get out of bed and leave the hospital. The writer knows of an instance in which a patient, in the active suppuration of confluent smallpox, succeeded in leaving the hospital and wandered through deep snow to a small ice-pond into which he waded. He was found after a few minutes, returned to bed, seemingly none the worse for his bath, and made a prompt recovery.

The Urine.—Arnaud found albuminuria in 95 per cent. of his cases, the amount varying from day to day. Auche et Jaucheres found the toxicity of the urine diminished in the stage of suppuration. Roger found albuminuria not common. It was present in 15 per cent. of the mild cases, in 25 per cent. of the discrete, and in 28 per cent. of the confluent. Welch and Schamberg found albuminuria in 84.47 per cent. of the fatal cases and in 50 per cent. of the cases which recovered. In over half of the cases in which it was present it was discovered on or before the fifth day of the eruption. Tube casts were found more frequently in fatal cases than in cases which recovered. They also found, agreeing with Arnaud, that there is great irregularity in the character of the urine. The urine would contain albumin and casts for several consecutive days, then perhaps on alternate days, and then might be free for a week or thereabouts, with a return a few days later.

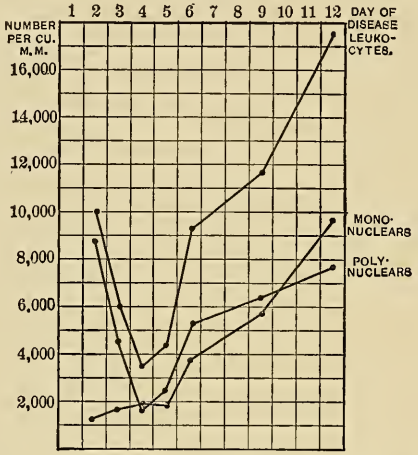
From our examinations of the kidneys, there was nothing to indicate any special influence exerted on them by the disease other than that due to the cytological blood changes. The degenerative changes were such as usually accompany acute febrile diseases and are associated with a varying degree of albuminuria. The cases of acute nephritis occurred late in the disease and were to be regarded as complications.

Leukocytes.—The blood examination in variola at certain periods may assist in the diagnosis. In a typical severe case in which the lesions become confluent on the face and which runs its course to recovery without complications, the leukocyte curve shows as a rule a normal number during the febrile remission, followed by a rise, reaching its acme on about the eighth day of the disease. It then declines slightly, rises again from the twelfth to the fourteenth day, and finally returns to normal during convalescence. During the remission, from 8,000 to 10,000 per cmm. will be found and at the height of the eruption from 12,000 to 16,000. An increase in the number of mononuclear cells is generally found, but the variations in the total leukocyte count are most influenced by variations in the number of polynuclear neutrophiles.

In very mild cases of variola vera the leukocytes do not exceed the normal limits. In cases of mild discrete smallpox the leukocytes may show only a gradual increase during the evolution of the eruption. In such a case the

increase in mononuclear leukocytes may be marked. In fatal cases there is a terminal leukopenia and the leukocyte count is highest at the time when the remission of the fever is due, ranging from 10,000 to 14,000 per cmm. Cases complicated by a pneumonia show no coincident leukocytosis.

FIG. 28.



Mild discrete smallpox. Recovery without complications. Eruption appeared December 21st. Discharged well December 31st. Onset severe, with delirium and convulsions. Remission on the evening of the third day, and from that time on no clinical symptoms were observed save the eruption. The skin lesions were few in number and principally on the face and legs.

In hemorrhagic pustular smallpox there is a great increase in the leukocytes. In purpuric smallpox there is marked leukocytosis. The lowest count recorded in four cases was 16,000 and the highest 46,200 per cmm. The mononuclear leukocytes are notably increased in number. Normoblasts are frequently found.

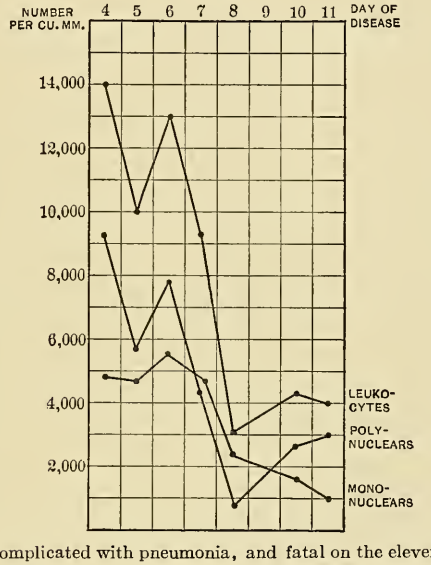
The study of the stained smears in all types of the disease show the more or less constant presence of cells belonging to the leukocyte series but which are not normally found in the circulating blood.

The phenomena of leukocytosis in general may be reduced to a matter of numerical cell equilibrium. The factors governing the leukocytes in the blood may be arranged under three heads: (1) Those influencing leukocyte motion, by which the adult actively amœboid neutrophile polynuclear leukocytes are removed from the blood into the tissues and from the blood-forming organs into the blood stream. (2) Those influencing cell differentiations, by means of which the adult cells are formed from the ancestral cell types in the hæmotopoietic organs. (3) Those presiding over cell multiplication, whereby a sufficient number of cells is formed, upon which the preceding factors may work.

Light is thrown on the condition of the peripheral blood by the examination of the tissues, and particularly of the blood-forming organs. One of the most striking things in the histological study of the smallpox process is the paucity of cells in the exudations. In the skin lesions there may be extensive degeneration of epithelium and abundant fluid exudation without the presence of a single foreign cell. Exudation cells appear only in a late stage

of the skin lesions, and are always fewer than would be found in any analogous process of degeneration and exudation due to bacteria. The condition so commonly found in skin lesions of all sorts, that of polynuclear leukocytes advancing between the epithelial cells to the area of lesion, is not met with. In the lesions of an acute endocarditis which developed in a case of hemorrhagic pustular smallpox, death occurring on the fifth day, no leukocytes were found in the exudation. Polynuclear leukocytes only appear in the lesions during the pustular stage. Mononuclear cells may also be seen in the pustule contents and around the vessels of the corium. In the very severe cases which die during the first week of the disease, one is struck by the absence of polynuclear cells in the vessels of all the organs. The mono-

Fig. 29.



Confluent smallpox complicated with pneumonia, and fatal on the eleventh day Patient more or less delirious while in hospital. During life no clinical evidence of pneumonia.

nuclear cells are present in great excess over the polynuclears. The preponderance of mononuclear cells in the vessels of the tissues is greater than is indicated by the differential counts made from the peripheral blood. It is now accepted that the polynuclear cells are formed by a process of differentiation from the myelocytes. This takes place in the bone-marrow chiefly. Under normal conditions the bone-marrow always contains an excess in the number of polynuclear cells. When there is a sudden withdrawal of these cells from the bloodvessels following injuries to the tissues, the cell equilibrium in the blood is restored, first, by the entry of the storage cells into the blood, and, secondly, by greater activity both in cell formation and differentiation in the marrow. In early cases of smallpox both marrow and spleen are depleted of polynuclear cells. In the early vesicular cases the marrow is not hyperplastic. The most numerous blood cells in the marrow are premyelocytes and large basophilic cells. Definite myelocytes are not numerous, and the forms with an incurved nucleus and which are generally

regarded as transitional forms leading to polynuclear leukocytes are also rare. Cells similar to those found in the marrow are also found in large numbers in the lymph nodes and in the spleen. In the lymph nodes they are found both in the follicles and in the sinuses. The cells here agree substantially with those found in the marrow, but are larger and their nuclei are more vesicular. Numerous nuclear figures are found in them In the spleen these cells are found both in the pulp and in the follicles. They are amœboid and in sections are often found in the act of passing through the wall of the vessel. The general type of the mononuclear cells in the blood is that of a basophile cell with a relatively large round nucleus which contains abundant chromatin. The cytoplasm varies in character, much depending upon the preservation of the tissue. The cells vary in size. In the smaller cells the cytoplasm is more compact and the granulation more evident than in the large. Nuclear figures are not infrequently found in these cells within the vessels, in situations where the circulation is not active.

From the study of the blood combined with the study of the organs it seems clear that the explanation of the peculiar mononuclear leukocytosis of variola is to be sought in disturbances in leukocytogenesis, and hence in accentuations or in inhibitions of one or all of the factors governing leukocyte supply. The variations in the mobile polynuclear leukocytes are primary and the mononuclear leukocytosis, due to the entrance of antecedent cells, is secondary and indicative of deficiency in the supply of the adult cell-types. This deficiency is, in turn, dependent upon the failure of cell differentiation and multiplication in the antecedent extravascular leukocyte series, which is in part due to outward passage and in part due to destruction incident to the disease. The analysis of the cell components of the leukocytosis indicates, at first sight, that not only cells of the polynuclear neutrophile series are involved, but also those of the lymphocyte series. The large mononuclear eosinophiles and mast cells are not affected. The cells are essentially all of the polynuclearneurophile series. The most common type of cell found represents a cell remote in the series of differentiation.

Complications and Sequelæ.—These are frequent, although none are in any way peculiar to the disease but are such as we would expect to find in accordance with the character of the pathological lesions. With the beginning of suppuration the specific character of the disease is over. There remains a suppurative process of great extent, usually with streptococci in the foci of suppuration. These foci offer favorable conditions for absorption and blood infection by the bacteria. Not only the skin but many of the mucous membranes are affected. No sharp line can be drawn between the complications and sequelæ. We should expect to find complications due to the action of the specific toxic products of the cytoryctes. Most of these are included in the delirium and other symptoms of the initial stage. It is probable that there are others which appear later in the disease such as the specific orchitis. Notwithstanding the extent of the injury which is produced in the testicle, these do not give rise to symptoms, and no permanent injury seems to be produced; or, if so, it has escaped notice.

Among the most common complications are boils. These add much to the suffering and often have a very protracted course, crop after crop succeeding one another. They are due in some cases to direct extension of the infection from the pustule, in others to the usual method of hair follicle infection from the surface. There may also be deep subcutaneous abscesses and diffuse

spreading suppurations which may bring about a fatal termination. These suppurative skin complications commonly appear during the crusting stage, and are accompanied by elevation of temperature.

Erysipelas is not common. When it does occur, it comes on in the third week of the disease. Considering the numbers of streptococci which are present in the lesions, and the opportunity for infection, it is surprising that this affection is not more frequent.

Complications affecting the respiratory apparatus are common. The extensive, deep, and destructive ulcerations of the larynx, which sometimes occur, are fatal. In other cases the superficial specific laryngeal lesions may produce cicatrices and deformities which affect the voice. Lesions in the lung varying in degree are so common that they form rather symptoms than complications. They are more common in the severe than in the light cases. They consist chiefly of foci of bronchitis and bronchopneumonia. They are due to streptococcus and often pneumococcus infection by the bronchi. True lobar pneumonia is uncommon, and is to be regarded as an accident and not related to the disease. In our 54 autopsies it was found in but 2 cases. The foci of bronchopneumonia may be so extensive as to simulate lobar pneumonia. Empyema is also uncommon, and is to be regarded as due to an infection of the pleura from the lung and not to metastasis.

Diphtheria has probably played a considerable role in some epidemics in the past. It is probable that some of the conditions which Eppinger described were due in part at least to this. In one of our cases there was an infection with the diphtheria bacillus, producing characteristic lesions of the pharynx and uvula. There are also found deep and superficial necroses of the soft palate and the pharynx, which are not accompanied by membrane formation. Curschmann found this most frequent in the hemorrhagic type. The infection easily extends to the salivary glands.

Bed-sores are not uncommon, but not as frequent as we should expect from the condition of the patient. They were far more common in the past, when the care was not so good. In addition to these, gangrene of the skin, often of considerable extent, may develop during the suppurative period in severe cases of confluent smallpox. This is superficial and seems to be due to the stasis of intense congestion. Such cases generally have a fatal termination before the demarcation of the gangrenous area is apparent. Noma following acute parotitis was seen in 3 cases in the Boston epidemic.

Complications affecting the eyes are common. In the prevaccination period, blindness was a common result. Pock formation, though common on the lids, is uncommon on the conjunctiva, though it undoubtedly occurs. The conjunctivitis is due to the infection with pyogenic bacteria combined with the retention of the secretion and the circulatory disturbances brought about by the tightly closed lids. The swelling of the lids may be so extreme as to render the opening of the eyes impossible without incision of the canthus. Ectropion may result from contraction of the cicatrices of the lids, which follow the pocks. When blindness results it is due either to corneal ulcers, which may perforate, or to pock formation on the conjunctiva at the edge of the cornea. A true pock formation of the cornea does not take place, which is one of the best evidences of the dissemination of the organisms by the blood stream. The writer has seen, however, a true pock form in a vascularized cornea, which did not differ from the common lesions on mucous membranes. The external ear may be the seat of pock formation just as the

skin elsewhere. The swelling may be so great as to occasion much pain and completely close the external meatus. Otitis media is not common when we consider the extensive inflammation along the Eustachian tube, and is more frequent in children than in adults.

Metastatic purulent inflammations of the joints are sometimes seen, especially in children. The elbow joint is most frequently affected.

Heart complications, either of the pericardium or endocardium, are rare. Endocarditis of the mitral valve was found in 1 of our autopsies.

Nephritis is not common. This does not include the almost constant degenerative lesions and the frequent acute interstitial changes, which latter have little clinical importance. When nephritis occurs it is a late complication. In our 54 autopsies 7 cases were found—2 of acute suppurative nephritis and 5 of glomerulonephritis.

The complications and sequelæ affecting the nervous system are numerous, and have received much attention. An excellent account of them is given by Immerman. There is very little anatomical change found in the nervous system. Southard, after careful study of the cortex, found no lesions. Focal lesions, consisting of hemorrhage and inflammation, have been described in both the brain and cord. The sudden hemiplegia and more partial paralysis which occur rarely in the course of the disease are to be attributed to such focal lesions.

Affections of the cord are more common than of the brain, the most frequent being motor paraplegias. These are not confined to severe cases, but are nearly as common in mild attacks. They may appear in any stage of the disease, and have been described as occurring in the stage of incubation. The paralyses occur suddenly; the bladder and rectum may be involved but sensation in the affected area may remain. Cases have been described in which the paralysis assumed a rapid, ascending character, giving the clinical features of Landry's paralysis. Post-variola paralysis of the palate and pharynx have been described. It is unknown in such cases whether there was not a mixed diphtheria infection.

Smallpox is one of the infectious diseases in which infection of the fœtus in utero takes place. Such cases are comparatively rare, but undoubted. Infection may take place at any time after the fourth month. It may take place earlier and the fœtus perishes and is expelled before signs of the disease are evident. The fœtus apparently passes through the typical stages of the disease. It may pass through the entire disease in utero and be born with the resulting cicatrices and possess immunity; or the eruption may appear a few days after birth, or be perfectly developed at birth. There have also been cases apparently well substantiated in which the fœtus in utero has contracted the disease without infection of the mother. Such cases can be explained only on the assumption that the disease in the mother was so mild as to be overlooked. There would be no possibility of the infection of the fœtus save through the maternal circulation.

Some of the cases regarded as fœtal infection are not true infections. One such case occurred in our autopsies. The mother died on the thirteenth day of the disease and showed an abundant, partly confluent pustular eruption which was crusting in places. The child was well developed and nourished. The skin of the neck, shoulders, arms, chest, and back, presented small closely-set elevations, from pin-point to half a millimeter in diameter, with a transparent vesicular centre and a white opaque border. The lesions were

largest and most marked upon the backs of the hands The general surface of the body was covered with a moderate amount of vernix caseosa. The general color of the skin was dull violet. The microscopic examination of the skin showed absence of true lesions. The vesicles were due to the elevation of the epidermis (or rather of the horny layer) by an exudation. The lesions were of the same character as the vesicles, which are rarely found in conjunction with the specific eruption. The testicles and bone-marrow showed the lesions which the writer regards as characteristic. No cytoryctes were found in the lesions. The condition of the fœtus was regarded as due not to a true infection, but to the action of toxic substances which developed in the mother and passed through the maternal circulation.

The writer has examined the skin from two others, in which the lesions were typical and contained the parasites in the same relation as in the adult. There seems no doubt that the specific organisms can pass through the placenta. Whether in these cases there are hemorrhages in the placenta by means of which they gain entrance into the fœtal blood is unknown. The character of the disease in the mother has no influence on the infection, though it has an influence on the life of the fœtus. Infection of the fœtus can take place as readily in a mild as in a severe infection of the mother. It does not take place synchronously with the maternal infection. It is not possible to accurately determine the date of the fœtal infection, but it appears to be about two weeks after the maternal infection and to take place at about the period of onset. It is probable that at or just preceding the onset there is the greatest amount of infectious material in the blood of the mother. The general opinion is that the immunity acquired by the mother is not transmitted to the child. Vaccination of children whose mothers had passed through the disease in pregnancy has proven successful in the majority of cases. There have also been cases in which the infection of the infant has taken place at birth, the eruption appearing sixteen days afterward.

Diagnosis.—The diagnosis of smallpox may be very easy or very difficult. There is no difficulty in the diagnosis of a well-marked case in the vesicular-pustular or the pustular period. It is not possible to make a diagnosis in the initial stage. Even the most typical onset and initial stage may be paralleled by other acute febrile diseases. The prevalence of an epidemic or the history of exposure may awaken suspicion. In the intervals of an epidemic it is not likely that the initial symptoms will suggest smallpox unless the physician have a personal and extensive knowledge of the disease. The prodromal rash is not sufficiently common to give much help. A petechial eruption occurring on the abdomen below the umbilicus, and extending to the groins, on the second day after a sudden onset with chill, nausea, and headache, is absolutely distinctive when it occurs. The diagnosis can always be made after the specific eruption occurs, even though it be scanty. There may be doubt between variola and measles. Apart from the history of preceding catarrhal symptoms in measles, which are absent in smallpox, and the different course of the fever, which in smallpox diminishes with the appearance of the eruption while in measles it increases, a careful examination of the eruption will decide. It must be remembered that the eruption of smallpox, even though it may appear in the beginning to naked-eye examination to be papular, really is not so, but is vesicular from the beginning. The vesicular character is usually most evident where the skin is thinnest, particularly on the scrotum. The use of a magnifying-glass in a

bright light is often of material assistance in determining the vesicular character. The apparent papules rapidly become vesicles, while the measles eruption remains papular. Moreover there is in measles a marked tendency for the lesions to arrange themselves in groups, and the presence of Koplik's spots is a great aid.

The greatest difficulty is in differentiating smallpox from varicella. Even an observer so accurate in most respects as Hebra held to the unity of the two diseases. Both are vesicular. In both the seat of the lesion is in the epidermis. When the vesicles of chickenpox are completely formed they are more sharply elevated, rounder, and more translucent than in smallpox. The fluid is contained not in a system of cells, as in smallpox, but in a cavity which can be emptied by a single prick. This is a valuable diagnostic sign. In varicella the lesions develop much more rapidly than in smallpox. The vesicles usually remain with clear contents and do not change into pustules. The lesions in the mucous membranes have much similarity in both. No doubt should arise in differentiating between the florid eruption in the two diseases. It is only in the beginning that doubt may come. In varicella the vesicle arises on a hyperæmic base which precedes it. There is never the hard shotty feeling of the vesicle in chickenpox which is so marked in smallpox, and which is due to fluid being enclosed in the small spaces in the epidermis. The initial stage of varicella is not so definite as in smallpox, is shorter, and the headache and pain are absent. Varicella may, however, begin with a definite chill and symptoms resembling those of mild smallpox.

The chief difficulty is in distinguishing between abortive smallpox, in which the eruption remains in the vesicular stage, and varicella. These abortive cases may have a very mild and almost unnoticed onset and initial stage, and no more constitutional disturbance during the eruption than in chickenpox. In such cases a very close study of the eruption will usually decide. If not, the patient should be isolated and watched. It is these cases which have led to the confusion between the two diseases and caused Hebra and others to deny the duality of smallpox and chickenpox The course of the eruption should decide, because even in the most atypical cases of smallpox there is not so sudden and complete drying of the vesicles as in chickenpox, and the scab from smallpox is always firmer and more elastic than in chickenpox, which gives a granular easily disintegrated scab.

Confusion has also arisen between pustular syphilis and smallpox. The diagnosis may be very difficult and impossible when the pustular syphilide is well marked and the smallpox mild with the pustules in full flower. The presence or absence of slight fever will not decide, for though usually present in smallpox and absent in syphilis, the conditions may be reversed. In the course of twenty-four or forty-eight hours it is usually possible to decide, for in smallpox the eruption presents almost the same degree of development all over the body, whereas the rash of syphilis does not. They do not pass through the typical vesicular stage of the smallpox pustule and do not change so quickly. With expert microscopic aid it should be possible to make a diagnosis at once, for in the contents of the syphilitic pustule or in scrapings from its base the specific organism, the *Spirocheta pallida*, will almost certainly be found.

Some have found difficulty in distinguishing between smallpox,pemphigus and impetigo contagiosa. In pemphigus the vesicles vary greatly in size; there is no basis of induration; the covering of skin is formed by the horny

layer alone and is much thinner. In smallpox in the vesicular stage, while the majority of the lesions might resemble pemphigus, certain lesions will almost certainly be found in the papular stage and others in the pustular. In impetigo contagiosa a close examination with section into the pustules should decide. They vary greatly in size and extent and the lesion is in the corium and not in the epidermis.

Doubts in diagnosis between acute glanders and smallpox may arise. This form of glanders is rare, and generally occurs in occupations which have to do with horses. In it abundant pustules may appear in the skin which have some similarity to the smallpox eruption. These may be abundant and chiefly seated on the face. The patient in this stage of glanders is more ill than he would be with a corresponding smallpox eruption. With the true pustules of glanders there may be combined vesicles which might be mistaken for smallpox vesicles; but they are due merely to the elevation of the epidermis by an exudation. The glanders pustule is a true abscess of the corium, and the epidermis takes no part in its formation. It arises as an abscess, is not so circumscribed, and beneath the finger feels more distant.

While the history and the fever may aid in the differential diagnosis of smallpox, only the eruption is decisive, and then only for one who knows the disease. There are two methods which will decide the diagnosis for any one, though they involve delay. One is by corneal inoculation on the rabbit. It is sufficient to prick the cornea with a needle which has on it contents of a smallpox pustule or vesicle. In forty-eight hours there will be slight opacity at the point of inoculation, and on microscopic examination swelling and proliferation of the corneal epithelium, with numerous cell inclusions, will be found. A more rapid and equally certain method is by the direct microscopic examination of the suspected lesion. Care must be exercised in cutting it out of the skin. If the lesion be grasped with forceps and cut out with scissors the histological details will be obscured by the compression. If the skin be frozen or injected with cocaine, this also will obscure details. A fold of skin should be grasped with the fingers beyond the lesion, bringing this to the summit of the fold, when it can be quickly cut out by a stroke of a sharp knife. The cut is almost painless and need go but little beneath the epidermis. By the modern rapid method of histological technique a diagnosis can be made in a few hours. No other pathological process gives the same histological picture as the smallpox lesion, and no other shows in the cells the characteristic parasite inclusions. In smallpox, as in any other disease, while in the majority of cases the diagnosis is easy, some will be found in which the diagnosis cannot be made without the employment of every aid, the most important of which may be time.

Prognosis.—It is impossible to give any general rules by which the prognosis of smallpox can be decided. It is influenced first by previous vaccination. Not only is infection in the vaccinated rare, but the severe forms of the disease are less frequent and the mortality lower. How greatly morbidity and mortality are affected by vaccination thoroughly carried out is apparent from the well-known statistics of Germany. It is impossible to determine whether a successful vaccination has or has not been performed. The statement of the individual that he has been vaccinated in infancy and the evidence of the scar is not proof of a successful vaccination. The scar is especially inconclusive. The writer knows of a college fraternity in which it was the custom to brand neophytes on the arm with a cigar. The resulting

cicatrices have often been exhibited to health officers and accepted as evidence of especially thorough vaccination. The cicatrices resulting from burns by strong mineral acids give the so-called typical foveated scar. In certain sections of the country in the last epidemic, it was not uncommon among the antivaccinationists to have nitric acid applied and to submit the resulting scar as evidence of vaccination. The regular depressions in the scar are evidence of the destruction of sweat glands and hair follicles, and it would seem possible that a successful vaccination might be so superficial that such a destruction and resulting pits would not result. Where a community is hurriedly vaccinated *en masse* we do not know in what proportion of the cases the procedure is successful. The only sure evidence of a successful vaccination is immunity.

The character of the epidemic influences the mortality. The pandemic of 1901 and 1902 in the United States was characterized by a remarkably low death-rate. There were, however, striking local differences. In certain places the mortality was almost *nil*, while in others it was as high among the unvaccinated as in the old epidemics. The statistics from the Municipal Hospital in Philadelphia (Welch and Schamberg), show great differences in the mortality of the unvaccinated. In 1871 and 1872 it was 64.41 per cent., in 1881 to 1885 it was 56.37 per cent., and in 1901 to 1904 it was 32.73 per cent. Even in the prevaccination period the same differences in mortality were seen. Cases of mild smallpox and smallpox without eruption were seen then in certain epidemics as they are now. The decline in the mortality of smallpox from that of the eighteenth century is to be attributed to vaccination solely. There is no evidence that the disease is growing progressively milder. The cases are progressively milder toward the end of an epidemic.

Variations in the period of incubation seem to have some effect on the prognosis. There is evidence that the period is much shorter in purpuric smallpox. Brinckerhoff and Tyzzer found that the incubation period was longer when the virus had become attenuated.

The character of the initial stage may effect the prognosis. A mild initial stage is indicative of a mild form of disease. A severe initial stage may be followed by a mild form.

The prognosis is influenced by the type of eruption and depends essentially on the intensity and extent. Starting from smallpox without eruption and mild smallpox, in which the mortality is practically *nil*, there is a steady ascent to the cases of purpuric smallpox with an absolute mortality. The mortality in confluent smallpox is always high, averaging 60 per cent. It is not always possible to predict the character of the disease during the vesicular stage, for the eruption may be abundant, simulating the beginning of a confluent case; but the vesicles may dry up, very few of them become pustular, and the entire fever and other phenomena of the pustular stage may be absent.

There is no evidence that race has any influence on the prognosis. The disease has always been extremely virulent in aboriginal tribes; but in the unvaccinated everywhere the mortality may be high. In ordinary epidemics the mortality is high among the negroes; but these are the most careless in regard to vaccination. Like most of the other infectious diseases smallpox claims a high mortality in drunkards. Sex, apart from pregnancy, has no influence. In pregnant women, the mortality is higher owing to the frequency of abortion, which is especially serious from the opportunities which are given for streptococcus infection.

All of the complications influence the mortality. Those due to extensive streptococcus infections of mucous membranes, with a possible septicæmia following, are especially unfavorable. The prognosis in the individual case can best be determined by an accurate knowledge of the extent and character of the disease and the effect it is exerting on important functions. The most lethal period of the disease is in the second week, at the height of the suppuration, and chiefly between the ninth and twelfth days.

Prophylaxis and Treatment.—It may be assumed that in any community, the disposition to smallpox exists and only awaits the reception of the germ. Prophylaxis consists in removing this disposition by vaccination and revaccination, and in preventing the infecting seed from reaching the favorable soil. In the absence of efficient compulsory vaccination we must regard every patient with smallpox as a possible source for infection. We are probably correct in assuming that the infectious material resides in the eruption; that it may be carried through the air, to how great an extent we do not know, possibly clinging to the dried epidermic dust; that everything coming in contact with the patient contains the infectious material; and that while it cannot increase outside of the body it may for a long time retain its infecting power. How long the virus retains its infectiousness is not known. Brinckerhoff and Tyzzer found that vesicle contents three weeks after drying on glass rods failed to give the corneal reaction, though sealed in capillary tubes it retained its virulence after three weeks. The virus appeared to be destroyed by putrefaction. These experiments are of course inconclusive. The evidence is that the disease is most infectious during the height of the eruption, but that it may be infectious at any period.

Isolation of the diseased individual is imperative, and is easy to carry out in the severe cases. It should extend to all cases, since the mildest attacks may be the source of the most virulent type. Individuals with very mild attacks are not clinically ill. They can proceed with their ordinary occupations and it may not be suspected that they have the disease. It is known that patients of this sort often play an important part in spreading the disease and may be themselves unconscious of any illness. Isolation can be carried out in a private house, but is difficult. It is very much better that the individual be taken to a hospital in which there is special provision for smallpox. The most ideal arrangement would be to have a smallpox division as a part of a hospital for infectious diseases. It should consist of simple barracks isolated from the other part of the hospital. In a large city, single cases of smallpox will almost constantly occur and should be cared for in a part of the hospital which is always in operation. There should be capacity for indefinite extension during periods of epidemics. Generally the smallpox hospital of a community is used only in the event of an epidemic and is unprovided with laboratories and opportunities for clinical and pathological investigation. Clinical teaching, the great stimulus to study, has no place in it. The energies of the physician in charge are entirely taken up in controlling the exigencies of an unusual situation. There is not the constant opportunity for comparison with other forms of disease. The hospital should be used for teaching because it is imperative that physicians should know the disease from clinical study.

Not only should the individual with the disease be removed to a hospital, but this should be provided with arrangements for taking charge of and detaining those who have been exposed to the infection. Every one who

has been exposed should be at once vaccinated; or, if it should happen that it is impossible to procure vaccine material, all persons never vaccinated should be inoculated with smallpox. If vaccination be performed immediately after the exposure, the vaccine immunity will develop in time to protect from the disease. It may be successful up to the fourth day after exposure, but rarely beyond. When performed later, both vaccinia and smallpox will run their course independently. From the experimental work of Brinckerhoff and Tyzzer there is evidence that the immunity of inoculated smallpox in the monkey develops more rapidly than that of vaccinia, but the evidence is not sufficient to justify resort to inoculation when the exposure is known to have been previous to four days. The vaccination of these detention cases should be thorough, and repeated if unsuccessful. They should be released after successful vaccination, and, even if this is not successful, after sixteen days, provided they have not again been exposed during the detention. They should of course be watched carefully, and in case of any suspicious symptoms at once be isolated. If there is the least doubt of the disease at entrance the patient should be isolated until all doubt is removed.

We do not know the life tenacity of the smallpox organism, and in the absence of this knowledge, it is best to assume that it is as resistant as bacterial spores. All measures of disinfection should be so thorough as to destroy spores. As present disinfection can be so thoroughly carried out that there is no necessity for the destruction of all articles which may have been infected. Nurses and others in constant attendance on the disease should be isolated. It is possible that physicians, students and others coming into the infected region may carry the infection to others. It is recommended that they should put on a long clean gown over their clothing and cover the hair with a cap. It would seem on theoretical grounds that this should afford some measure of protection; whether or not it does we do not know.

The smallpox patients should be detained until all the affected epidermis is removed. We know that the dried disks contain infectious material. These will remain longer when enclosed in the thick epidermis of the palms and soles than elsewhere, and their artificial removal will assist in the cleaning process. The patient should then be scrubbed clean in a bath to which some carbolic acid may be added, given clean clothing, and discharged.

In any case it must be remembered that our means of warfare against smallpox is not isolation and disinfection, but *vaccination.* All other means may be helpful; but *vaccination is the one essential.*

There is no specific treatment for smallpox. There are certain conditions in the patient which may be benefited and certain distressing symptoms which may be alleviated, but it is doubtful whether by means other than care and good nursing the course of the disease can be influenced. With the great variations in the character of epidemics, it is easy to see how methods of general and local treatment should have arisen, been supported for a time, and then supplanted by others. How numerous, how absurd and often injurious, these specific modes of treatment were, is abundantly told in the literature of the disease.

It is important that the patient be given an abundance of air space; that the air be frequently changed and the temperature kept low. The patient in the suppurating stage is covered with a putrescent mass of necrotic epidermis and exudation, which gives rise to a penetrating and highly un-

pleasant odor. This is not peculiar to smallpox, but may be found when the same conditions are present. The foul, stinking atmosphere of a hot and ill-ventilated smallpox ward almost certainly has a deleterious effect.

In the initial stage of the disease treatment may be necessary for the relief of the distressing pains. These can in a measure be controlled by sedatives or even morphia. In case of delirium and great nervous excitation Immerman recommends protracted warm baths. The fever is ordinarily not sufficiently high to demand any measure such as the systematic cold bath. Sponging with cool water is often grateful to the patient. The common fever mixtures, if not unpleasant to the patient, will do no harm. The headache may be relieved or benefited by the application of cold cloths or ice-bags to the head.

With the decline of temperature and the general amelioration of all symptoms during the primary eruptive stage no treatment is necessary. If the case promises to be severe the hair should be cut off. It usually comes out after the disease; and the eruption on the scalp is rendered more trying by the presence of the hair, as it becomes matted and foul with the discharge. Easily digested food may be given in accordance with the desires of the patient.

It is not certain that the course of the eruption can be favorably influenced by treatment, local or otherwise. The old method of puncturing the pustules to avoid cicatrices is now given up. Cicatrices are sure to result if the destructive process extends into the corium. Mercuric lotions and plasters have been recommended, also vaseline and oily substances, but these measures seem to exert no influence. Painting the surface with tincture of iodine has been recommended. It has been claimed that it causes a rapid desiccation of the lesions; Welch and Schamberg recommend it. The tendency is now to use those local measures which will at the same time give most comfort to the patient. When the eruption is especially thick over the face, much comfort is experienced by the use of cold compresses, which should be frequently changed. The moisture prevents the formation of the mask of crusts, under which a process of deep pyogenic infection may take place; and the exchange of the compresses removes the exudation. Such compresses often afford great relief to the tense, swollen hands.

The mouth and throat demand attention. In severe pharyngitis the application of ice to the neck often gives relief. If the patient is able to do it, gargling with astringent and antiseptic liquids is beneficial. In other cases some attempt may be made to clean the mouth by wiping it out. The eyes should be constantly examined; the swollen lids forcibly opened and the conjunctiva looked to. Conjunctivitis if present should be treated with nitrate of silver preparations, and thorough cleanliness is imperative. The matting of the crusts can be prevented by smearing the edges of the lids with vaseline. Cold applications to the lids are often grateful.

It is always important that traumatic disturbance of the eruption be prevented. The itching is often intense, especially toward the end of the suppurative period, and forcible restraint may be necessary, especially in children.

There is and will always remain much difference of opinion regarding the efficacy of alcohol. It has been highly recommended, especially in the period of suppuration. Immerman advises the use of full doses of alcohol and quinine, and thinks that such treatment is of actual service. Welch and

Schamberg also recommend alcohol, giving patients with confluent smallpox up to twelve ounces daily. There is not much to hope for from the serum treatment of the disease. It is perfectly true that the blood-serum, when immunity is established, will destroy the specific organism. It also seems true that the blood immunity is established before the eruption takes place and that its appearance is marked by the onset. All the phenomena attending this seem to indicate the action of a toxic substance which may suddenly appear in the blood, being set free by the destruction of the organisms which contain it. The eruption is due to the organisms which have been deposited in the skin, where they developed removed from the full action of the immune blood. The constitutional effects are not to be explained by the assumption of absorption of a specific toxin, but to the effect of the accidents of an extensive suppuration complicated by bacterial infection. If this be true, the only time when the serum bearing the immune factors could be used to advantage would be in an early period of the stage of incubation. No results have hitherto been gained by the use of serum.

The exposure of the patient to the influence of light of various sorts has not given the results which were hoped for.

CHAPTER X.

VACCINATION.

By GEORGE DOCK, M.D.

Definition.—Vaccination is the inoculation of vaccinia, by means of the virus of cowpox, and has for its object the production of a pock, with general symptoms, followed by more or less complete immunity against smallpox.

History.—The practice of vaccination we owe to Edward Jenner.[1] Under the name of cowpox certain diseases characterized by vesicular or ulcerating lesions on the udders of cows have long been known in England, and under corresponding names in other countries. The name was not limited to a single disease, but applied to various diseases that have nothing in common but vesicular lesions. In some cases, however, the disease has the characteristics of inoculated variola or vaccinia; it spreads from cow to cow in dairies, and when it once enters a stable usually affects the majority of the animals unless they are immune from a previous attack. Jenner originally supposed that cowpox was derived from "grease," a disease of horses' heels, and that, transferred by dairymen who dressed the horses' heels and also milked cows, the virus became more fixed in the cows. Grease or "greasy heel" is a term still applied by horsemen, but is probably rarely a variolous disease. Some early strains of vaccine were derived from what was called grease, but it is generally assumed that in some cases the horses had variola, and this of course would readily be conveyed to cows when the same persons handled both kinds of animals.

As regards the cowpox, the probability is that this, in its specific form, is variola, derived directly or indirectly from human sources. The term "spontaneous" applied to some cases of cowpox is a bad one, since there is no reason to think that cowpox arises spontaneously any more than smallpox. As a rule the source cannot be found; but if we remember the tenacity and the wide spread of smallpox, the relation can hardly be doubted. Numerous experiments show that, while failures may occur, it is comparatively easy to infect many species of animals with variola or vaccinia.

It was known to dairy-workers long before the time of Jenner that cowpox protected against natural or inoculated smallpox In various parts of the world, at different times, a number of persons made experiments with the inoculation of vaccinia in order to protect against smallpox. None of these detract in the least from Jenner's claim to immortality, for none of them led to a wide or general use of vaccination. Although his observations and experiments were few in number, they were more numerous than those of his forerunners, and were carried out with a scientific accuracy far ahead of the contemporary knowledge of infectious diseases. Jenner's work was based on the recognition of the traditions of the dairies, and in the hope of

[1] "The Works of Edward Jenner and their Value in the Modern Study of Smallpox," by George Dock. *New York Medical Journal*, Nov. 29 and Dec. 6, 1902.

announcing a discovery of value to the human race, *viz.*, a more manageable, less dangerous, and more certain protection than variolation. Formerly a rare operation, Jenner made it of world-wide use, and showed the possibility of carrying the virus through the human body and becoming independent of natural cowpox, an essential step in the development of vaccination.

Jenner's first work, *An Inquiry into the Causes and Effects of the Variolæ Vaccinæ*, appeared in the summer of 1798. Its reception at first was lukewarm; but a controversy soon sprang up and Jenner published additional observations and conclusions early in 1799. From this time progress was rapid. Before the end of 1799 several institutes for cowpox inoculation were established. In 1800 the operation was carried out in most parts of Europe, and in America, where Waterhouse of Cambridge had taken it up with enthusiasm; and it was used very early in the world-wide Spanish colonies.

Very early Jenner established the following points: The protection of vaccination against smallpox, whether acquired in the natural way or by inoculation; the importance of using virus only from typical and regularly progressing vesicles free from suppuration or other complications; the advantages of a clean and simple operation; the possibility of partial or complete failure, with the indication for repeating it (or in case of need even variolating); the importance of special knowledge, experience, and careful observation in all cases. He realized that severe local lesions do not indicate protection but may even be harmful. Jenner's great error was his belief in the life-long immunity conferred by vaccination; and yet if it had not been for this fallacy he probably would never have given vaccination to the world. The consequences of the error have not yet been overcome by the medical profession; but for this Jenner should not be held responsible.

Coincident with the rapid spread of vaccination was a marked fall in the extent and mortality of smallpox all over the civilized world. As an example, in London in the years 1761–1800, the mortality in the successive decades was respectively 24,234, 20,923, 17,867, 18,477. In the first two decades of the 19th century it was 12,534 and 7,856. Toward the end of the second decade of the 19th century smallpox began to increase, and in some countries became almost as prevalent as it had been before. The causes of the recrudescence are not difficult to understand. Many people had been vaccinated so long before that they had lost their immunity wholly or in part. This was the time to settle the question as to the life-long protection which the early vaccinators so fondly believed in, but prejudices were still too strong. Many other people were not vaccinated at all, because smallpox was so much less frequent that the operation seemed unnecessary, and there was a smaller proportion than before not protected by smallpox. Smallpox virus existed in many places. No efficient effort had been made to stamp it out, and it was even kept up by sporadic variolation, not prohibited in England until 1840, five years later than in Prussia. Whenever the disease prevailed some vaccinated people were sure to take it, and many were the efforts to reconcile this with the sweeping claims of the early vaccinators. Imperfect vaccination, degeneration of lymph, new types of disease, the cowpox not the genuine kind, or the smallpox not real smallpox—such were the explanations made; but the practical lessons were very slowly taken up. Looking back it is clear that certain great changes had occurred in the smallpox situation since Jenner's discovery. The absolute mortality was less;

the disease was not so frequent as before in the years following the usual age of vaccination; and these facts were most obvious in countries that had the most thorough vaccination. The change in the age-incidence is interesting. Smallpox was commonly spoken of in Germany in the pre-vaccination days as "Kinderpocken." Of 1,252 cases of smallpox before vaccination, 94 per cent. were in children less than ten years of age, and no case above twenty. Of 1,677 cases after vaccination only 18 per cent. were under ten years of age, and 42 per cent. over twenty. Epidemics were smaller, and mild cases, long known but rarely mentioned, became relatively more frequent. The recognition of varioloid as a mild but genuine form of smallpox was a great advance over the time not long before when each variety of smallpox was looked upon as a distinct disease, not protected against by vaccination.

In this period revaccination began. Suggested early in the century, it was long neglected. Certain German states first applied it to their armies. Würtemberg, after a trial in 1829, made it obligatory for recruits in 1833; Prussia in 1834. Some other German states did not adopt it until the 60's.

The most striking test of the possibilities of vaccination was made in the war of 1870–71, and depended largely upon the farsighted care of the German military authorities. Smallpox became so prevalent in France in the preceding winter that efforts were begun to combat it, but the outbreak of the war not only prevented such action, but as usual caused a great increase of the disease, which rapidly extended over Europe. In Germany, where many prisoners of war carried the infection, the disease was widespread; but it was a striking fact that the German soldiers were not only less frequently and less severely affected than the French, but that they were less affected than civilians of military age in the same towns. The only difference was that all the German soldiers under arms at the outbreak of the war had been revaccinated within two years. The following figures show the mortality of different classes at that time: revaccinated 5 per cent., once vaccinated 14 per cent., unvaccinated 45 per cent. This object lesson was not lost on the newly formed German Empire. In 1874 the first law was passed providing for the vaccination of every child before the end of the second year, and of all school-children in the twelfth year. The result of the operation was to be a matter of record, and failure to produce a satisfactory vesicle necessitated a repetition. In the civil population the mortality sank rapidly so that in 1899 the deaths in the whole empire were only 28, scattered over 21 different places. In the army, too, the death-rate became lower than before, showing the protective influence of widespread vaccination, since the soldiers had been vaccinated in the same way for forty years before.

In the meantime other important events had taken place. The continued existence of smallpox was ascribed to degeneration of lymph, and this was sometimes obvious in the poor development of the vesicles. This led to efforts to obtain stronger virus. Cowpox had become very rare, and though rewards were offered in some countries, few cases could be found. Retro-vaccination, or the inoculation of the cow with human virus, was used to revive the stock, but not with the desired success. Numerous experiments since the time of Gassner (1807) demonstrated that vaccinia is variola in the cow. Inoculation of calves with smallpox material, with proper care, produces a disease indistinguishable from primary or "spontaneous" vaccinia, and giving the same protection against both smallpox and vaccination that natural cowpox gives. The contradictory results of the oft-cited Lyons

commission, which believed that variola inoculated into animals remained variola, with all its dangers, are now universally believed to have been based on technical errors. Inoculation of the first remove of such material is likely to produce severe effects, such as intense local reaction, general eruption with secondary fever, or even death (Chauveau). But after several transfers through cows the contagious character is lost, secondary fever does not follow inoculation, and the material can be made to retain its characters without bad results.

Etiology.—Since vaccinia is then believed to be smallpox, altered by its passage through the cow, the etiological factor must be the same, modified in virulence if not in morphological characteristics. And in fact the history of the search for the cause of vaccinia is part of that of smallpox. Like the latter, vaccine has been investigated in vain by all known methods for specific bacterial forms, but none have been found. Finally, after various indefinite alleged parasites were found, the bodies first clearly described by Guarnieri, called by him *Cytoryctes variolæ seu vaccinæ*, have been identified by all who have repeated his observations, although they have not all come to the same conclusion as to details or biological position. Wasielewski (1901), and especially Councilman (1903) and his fellow-workers, have done the most thorough work, and that of Councilman is important not only because of his great experience with problems in pathology requiring the same methods, but also because he was led to think that the "intranuclear" phase of the parasite found in smallpox does not occur in vaccinia, where the intracellular or cytoplasmic forms are constant and numerous. "The cytoplasmic cycle is simple, and no forms can be found in it which can be interpreted as sexual." The intranuclear forms, much more complicated, are probably sexual, according to Councilman.

An important contribution was made in 1904 by E. E. Tyzzer,[1] who used rabbit's corneas, inoculating them with vaccine lymph and also with variola lymph. He also inoculated calves and sheep, the latter with negative results. Control work was carried on by injections of bacteria, applications of chemical and other irritants, inactive vaccine lymph, and various toxins. The vaccine body as described by Tyzzer has a resemblance to many of the bodies found in various diseases and often rightly considered degeneration products. He thinks, however, that there are certain morphological features by which their parasitic nature may be recognized, and in this he has the support of Councilman and Calkins.

The bodies are found in the inoculated cornea, skin, and mucous membrane, as early as sixteen hours (cornea), and are then of small size. They become more numerous and at the same time increase in size, and in course of time are found farther away from the point of inoculation, but also smaller than the older ones nearer the centre. In the smallest forms details of structure cannot be made out. They occur in the cytoplasm of epithelial cells, and also occasionally between cells. The smallest bodies are about 1μ in diameter, and stain more intensely than the cells. So far no specific stain has been discovered. Slightly larger forms are found often near the nucleus of the cell, or in the perinuclear space. Wasielewski regards the clear space as an artefact, due to the shrinking of the cytoplasm away from the nucleus and the vaccine body. Tyzzer doubts this. As the

[1] Tyzzer: *The Journal of Medical Research*, vol. xi, p. 180.

bodies increase in size the structure becomes complex. A deeply stained granule can be seen within the body. As it becomes larger an unstained area appears surrounding the granule, the areas being larger than the similar areas around most other cell inclusions. In the rabbit's cornea at this stage the body measures from 5 to 7μ—10 or 11 in the skin and mucous membranes. In the calf the bodies are smaller, rarely exceeding 4μ. The smaller forms vary much in outline; the larger ones are usually rounded or reniform. The central granule stains like chromatin. No nuclear membrane can be demonstrated. The rest of the body has a reticular structure and stains as cytoplasm.

After the body has reached a relatively large size the chromatin is more abundant and irregular. It may appear as a mass of granules, and in later stages the granules are separate and distinct. In other cases the granules are in the periphery of the bodies, within small masses projecting from the surface, and resemble mulberry forms or segmenting bodies. Other forms are found, suggesting segmentation, with a residual body. Cells containing the bodies are larger than normal, and "glassy," later vacuolated and hollow; but similar changes occur in cells not containing the supposed parasites. The nuclei of the cells may present various kinds of degeneration. Tyzzer excludes the possibility of error by confusion with degenerated red blood corpuscles, leukocytes, centrosomes, extruded nuclear material, and degenerations such as are caused by various infections. The morphological grounds for looking upon the bodies as organized parasites are, as Tyzzer says, very strong. He has not made observations on the motion of the bodies, which Wasielewski convinced himself existed.

Tyzzer concludes that the bodies are organisms with etiological relations to vaccinia, because—

"1. The bodies consist of a substance which resembles protoplasm in structure, and which always contains masses having the staining reaction of chromatin.

"2. The bodies show variation in form corresponding to a developmental cycle. They begin as small bodies of approximately the same size in the early lesions, increase in size up to a certain point, and then undergo segmentation (both the body and the chromatin) to form the small bodies like those from which the series began.

"3. All other hypotheses are insufficient to account for the presence of these bodies, their structure, and the changes met with in their growth and development."

Tyzzer leaves the more exact classification of the parasite to the future. He describes the pathological process in vaccinia as an infection of epithelial cells by the small forms. These getting near the nucleus grow larger, in time segment, infect new cells, and cause the enlargement and proliferation of the cells, with the production of an exudation secondary to the degeneration of the epithelium. It is impossibl to deny the probability of the conclusions of Tyzzer, but his figures do not lead to conviction any more than do the very similar ones presented by various observers in cancer, and by Löwit in leukæmia.

Ewing[1] (1904), came to conclusions at variance with those of Tyzzer. He first made an effort to distinguish between vaccine bodies and other cell

[1] *The Journal of Medical Research,* vol. xii, p. 509.

changes, and next to ascertain the differences that exist between vaccine bodies as found in rabbits and man, and those produced in other animals that may react to vaccine. In a preliminary study of material from autopsies on thirty cases of variola he found the vaccine bodies, but concluded they were probably cytoplasmic structures. In the study of the corneal vaccinia of rabbits he found various forms such as solid globules, reticulated bodies, and rings. The globules and rings were not unlike bodies that occur in the inoculation of the cornea with diphtheria toxin, but the reticulated bodies, which are evidently the same as those of Tyzzer, Ewing could not produce by any other agent than vaccine. He also found large bodies, occupying one-half to four-fifths of the cell, crowding the nucleus to one side, and showing granules around a central body Admitting the existence of transitions from small bodies to large ones, Ewing thinks it just as likely that these represent steps in the cycle of a degenerative process involving the cytoplasm of the epithelial cell. This he thinks is borne out by the direct connection of many of the larger reticulated vaccine bodies with the cell reticulum. Though most of the bodies lie free, he thinks this is due to artefact. The variable size of the granules is another objection to the idea of organized parasites. In short, Ewing thinks there is a specific vaccine body which may follow a definite cycle of development, but which is merely a degenerating portion of the cytoreticulum. He could not demonstrate amœboid motion in the bodies. His observations on the changes produced by vaccine inoculations in various animals led him to conclude that in vaccination there is an active diffusible toxin similar to that of diphtheria, a production not usual with protozoa. He also concluded that the "vaccine body is the particular form taken in some warm-blooded animal of a universal property of degenerating epithelial cells."

In a later paper Ewing[1] (1905) gives the results of the study of vaccine bodies in isolated cells, by means of "Klatsch" preparations from vaccinated rabbits' corneas. When such preparations are properly stained and examined they show first a thickening of several adjoining meshes of the cytoreticulum, close to the nucleus. The clear zone so striking in sections cannot be seen. Sometimes the body is continuous with the nucleus. The changes, then, do not resemble endoglobular parasites as much as they do certain forms of cell degeneration with the formation of "chromidial bodies," such as Hertwig has found in protozoa and Zuelzer in Difflugia urceolata. They are explained as due to the separation of the chromatin from the achromatic substance of the cytoplasm, under the influence of toxins.

These studies necessitate a re-opening of the question almost closed by the work of Guarnieri, Wasielewski, Councilman, Calkins, and Tyzzer. Ewing makes several suggestions. "It may be supposed that the cytoplasmic structure contains a submicroscopic organism; that this appropriates and alters the cell reticulum as a protecting nidus, and attracts nuclear proteids as nutriment." "Or, it may be supposed that the vaccine body belongs to that hypothetical class of parasitic microörganisms in which there is at one stage of development a fusion of the host cell and that of the parasitic organism, forming a mycoplasm. The theory of the latter, however, has not yet been firmly established.. Or it may be possible to find in the meshes of the vaccine body or in some of its stages a definite microorganism."

[1] *The Journal of Medical Research*, vol. xiii, p. 233.

The work of a number of investigators who oppose the theory of Guarnieri need not be quoted in detail. Suffice it to say that none of them, the most notable being Salmon (1897), Hueckel (1898) (who thought the bodies specific for vaccine, but not organisms), Roux, Borrel, and Sikorsky (1903), have successfully controverted the statements of the others quoted. Ishigami (1902) thought he had cultivated the parasites in a special medium containing epithelial cells.

Although bacteria are no longer believed to be the specific agents of vaccine, they are of great importance in the pathology and still more in the practical application of vaccinia. Lymph from young intact vaccine vesicles is sterile, but in lymph as ordinarily examined, bacteria of various kinds may be found, both in the calf and in the human vesicle. Most of them are harmless saprophytes, but pathogenic forms are not rare, though usually not very virulent, as the great majority of vaccine operations prove. Streptococci are rare, but have been found in the benign vaccine pustules in children.

The histology of vaccine lesions in human beings has not been as thoroughly studied as that of variola, but the investigations of Pohl-Pincus (1882), Unna (1882), and others, with those of more recent workers, such as Steinhaus, Wasielewsky, and Tyzzer, and more especially the studies of human vaccinia by Howard and Perkins,[1] give us a fairly clear idea of the process. It begins as a hyperæmia which increases in the purulent stage. Degeneration of epithelial cells, with swelling and vesiculation or reticulation, occurs, especially in the middle part of the prickle-cell layer. The remains of the puncture, if one has been made, show as a cleft filled with blood corpuscles, broken-down cells, and fibrin. Necrosis of cells forms columns that run down through the centre of the lesion, and the dropsical degeneration begins near these. The prickle-cells become smooth. At the end of twenty-four hours the epithelium shows swelling, but not macroscopically. Howard and Perkins found vesiculation far advanced at forty-eight hours. The reticulum, made up of fine and coarse fibers, can be traced to hyaline fibrinoid degenerated epithelial cells.

As the process advances, hydropic degeneration affects all the layers of the epithelium, and may extend to the corium. Nuclear changes then become more prominent, with numerous mitoses, often atypical, and with various forms of degeneration of the chromatin. At the margins of the vesicle the cells are often swollen and their prickles lost. Cell inclusions may be seen. Red blood corpuscles and leukocytes occur in the degenerated tissue at the base and sides of the vesicles, eosinophile cells being often numerous. Changes in the corium are more marked than in variola. Œdema, leukocyte infiltration, and vascular changes, are described by Howard and Perkins. The sweat ducts and hair follicles are often unaffected by the dropsical degeneration, though polynuclear cells appear in them, and the ducts, with the degenerated cells along the seat of inoculation, show as strands among the hydropic cells and account for the umbilication. By the fourth or fifth day in the calf (Steinhaus), the fourth in man (Howard and Perkins), the vesicle ceases to increase in diameter, but becomes elevated from liquefaction of its contents. In the liquid contents are broken down cells, free nuclei, and debris. As the epithelial cells liquefy, a gradually increasing immigration of leukocytes takes place, from about the third

[1] *The Journal of Medical Research*, November, 1905; vol. xiv, No. 1.

day, causing the contents to become turbid and purulent, and obscuring the histological features of the lesion. On the sixth day the pustular change is complete; the cellular strands begin to break down. On the fifth, sixth, or seventh day desiccation begins. The epidermis grows in from the sides, with numerous nuclear figures, gradually raising up the scab.

Tyzzer describes the changes in the cornea, the mucous membrane (nose), and the skin, in vaccinated animals. Howard and Perkins could find no bacteria in the lesions they examined from the second to the seventh day, and they conclude that mixed infection with bacteria plays no part in the production of the lesions of human vaccinia when the operation is carried out under proper precautions. These observers conclude that the degeneration and exudation "are due to the action of a powerful soluble toxin which acts very much like diphtheria toxin. It would appear that immunity production is intimately associated with the setting free of this poison in the lesion, for the œdema and other inflammatory changes persist long after the process in the epidermis has ceased to extend." According to Tyzzer, and also to Howard and Perkins, "The vaccine bodies are found constantly associated with the lesions, in the cytoplasm of epithelial cells, and in the ducts and gland-cells."

The Vaccine Virus.—Until late in the 19th century vaccine virus was derived chiefly from human vesicles and either used at once—"arm-to-arm"—or preserved in various ways. Sometimes the "crusts" or scabs were used, but must have been unsatisfactory, as they represent a stage of the lesion when specific activity is less and contamination greater than in earlier phases. Arm-to-arm vaccination in general gave good results; but it was difficult to keep up the supply regularly except in large cities, and even there the usual sources of lymph—foundling asylums—offered obvious risks. The difficulty of maintaining the supply and the danger of transmitting other human diseases made it comparatively easy to return to bovine lymph, but not to depend upon casual vaccinia. Retrovaccination, or the inoculation of cows with vaccinia, had often been resorted to in order to improve strains of lymph. Some early attempts at deriving supplies regularly from cattle were not received with favor, but in 1842 Negri began the cultivation of bovine virus in Naples, and continued it for many years. Lanoix introduced his methods and virus in Paris in 1864, but soon after substituted for Negri's virus that from a case of "spontaneous" cowpox discovered at Beaugency. Bovine vaccination was then rapidly adopted in various European cities, and in 1870 was begun in Boston, by Martin, who imported some of the Beaugency stock. It was introduced into Japan in 1874, in England not until 1881.

The virus was inoculated after the various methods practiced with human lymph, arm-to-arm vaccination being imitated by taking the calf with ripe vesicles to the house of the patient, or making direct inoculations in a central locality. This method was abandoned only a few years ago. The use of ivory slips or "points" coated with lymph represented a great advance over other methods before the principles of asepsis were well understood.

For various reasons, chiefly technical, vaccine "pulp" took the place of lymph soon after 1880. Pulp is the whole lesion, consisting of epithelial cells, leukocytes, red blood corpuscles, fibrin, fat, specific and non-specific microörganisms, and debris. The use of pulp is often objected to, but without good reason. It is said to contain more pus and more bacteria than

lymph, but pus should not be present in the vesicles when they are made into pulp; and it has not been demonstrated that the whole lesion contains more bacteria than an equal quantity of the liquid. The so-called lymph was often largely blood-serum; but even pure lymph has not been shown to exceed pulp in specific action. If the prevailing views of the cause and histology of vaccinia are correct, pulp must be superior. At present the bacteria can and should be controlled, no matter what part of the material is used.

The animals used for the production of vaccine are calves or heifers, females being generally preferred, and light-haired ones on account of their clearer skin. The age is usually three to six months, though it varies from one month to two years. The younger the animal the less is the danger of tuberculosis, or of a previous attack of cowpox, with immunity and loss of time and material. The animals should be sound and well, and, in order to avoid inoculation during accidental disease from travel or change of conditions, should be kept under observation for a few days. Tuberculin and other tests are unnecessary, as it is customary to kill the animals before the vaccine is used, and the autopsy furnishes more accurate information. Vaccination does not lessen the value of the animals for food.

The calves are cleaned as thoroughly as possible before they are taken to the operating-room. They are then fastened to a suitable table and the abdomen is shaved and washed with soap and warm water. Antiseptics have been used, but are not necessary. In any case the final washing is done with large quantities of sterilized water and the skin dried with sterilized towels. The operators, in sterilized clothing, observe the usual rules of asepsis. A series of incisions is made in the prepared skin, about one inch apart. The area treated varies in different institutions, sometimes extending from the inguinal folds to the level of the navel, sometimes to the axillary folds. Other areas, such as the escutcheon or the scrotum, are sometimes inoculated. The sides and back are not used on account of the toughness of the skin. If more than slight bleeding occurs it is checked by pressure with sterilized towels. The "seed" vaccine is spread over the prepared surface and allowed to dry. The seed is of various kinds, either glycerinated bovine virus selected with care from particularly well-developed vesicles and of tested bacterial purity, selected humanized virus, or material derived more or less remotely from human variola. Some of the best strains in Europe are of this kind. It would be of great scientific interest and some practical value to have records of all vaccine strains, but as it is, makers often do not know or are unwilling to state the source and nature of the seed.

Course of the Lesions on the Calf.—In a successful case the incisions show red borders in about forty-eight hours. On the third day a swelling appears, with a series of papular elevations. By the fourth to the sixth day the vesicles are usually well-developed. The incision causes a central depression that prevents the umbilication from showing well. The tops are whitish, the bases red around the vesicle. During this time the animals are kept in clean stalls and carefully observed. Dressings are not generally used. The vesicles are not easily ruptured in the early stages. The material is gathered between the fourth and sixth days, or at a time when the vesicles are well developed but show no evidences of suppuration. At the proper time the animal is again put on the table, the abdomen thoroughly washed with warm water and soap, rubbed by hand, finally washed with sterilized water, and

dried. This removes the dried superficial epidermal scales and does not break the vesicles. For the removal of the pulp a large curette is drawn along each row of vesicles, taking these off very thoroughly without much contamination with blood.

After the pulp is all secured, it is ground in a special mill under aseptic precautions, in order to render it homogeneous. It is then thoroughly mixed with glycerin and kept for several weeks to "ripen." The object of the glycerin is to destroy the bacteria, either in the vesicles at the time or accidentally introduced into the pulp and depending partly upon the care of the animals, partly on the thoroughness of asepsis of the institution. Glycerin was used with vaccine lymph very early, as by Cheyne, in 1850, to keep it fluid; by Mueller, in 1866, to increase the bulk; but it was not until 1891, when Copeman showed the effect of glycerin on vaccine and its contaminating bacteria, that its use became general. For some years before that many antiseptics were tried and abandoned.

Copeman proved that in glycerinated pulp the bacteria become gradually reduced in number, and even disappear at a time when the specific agent is still unimpaired. Drying has a similar effect on vaccine, but glycerin has the advantage that besides dehydrating the germs, it permits the formation of a homogeneous emulsion, part of which can easily be tested, and so permit accurate conclusions as to the qualities of a large amount of lymph. In glycerinated virus the specific action has been found present after as long a period as one year, but it may become inert within a month after the bacteria are killed, especially if the virus is exposed to ordinary summer heat. Great dilution does not destroy the practical efficiency of glycerinated lymph. The usual proportion is about one part of lymph by weight to ten parts 50 to 60 per cent. chemically pure glycerin, but dilutions of 1 to 2,000 have given good results. One calf may furnish 3,000 to 5,000 portions, and perfect vaccination has been obtained from lymph representing one-fifteen-thousandth of the yield. But this gives only the favorable aspect of the glycerin. Its effects on the bacteria and on the specific germs are modified by other factors. Glycerin acts best on bacteria at a temperature of 37° C. or above, very little at low temperatures; but the vaccine germs are injured by temperatures very little above 37° C., though they resist cold to a remarkable degree. Moreover, the bactericidal action of the glycerin is very imperfect in practice, so that careful tests are necessary, even if the ripening has been carried out the usual time of four to six weeks.

Valuable as glycerin has been, it does not obviate the need of scrupulous cleanliness, and until we are able to cultivate the specific organisms pure, efforts should be made to find a better agent. Such efforts have in fact been made. Green (1903) showed that chloroform vapor eliminates the bacteria while leaving the specific elements fully potent. According to Green's modified methods (1904) a current of air containing chloroform vapor is passed through the emulsified virus for one and one-half to two hours, the inlet and outlet tubes are clamped, and the material put in the ice-chest for eighteen to forty-two hours. Or the current may be continued for six hours, and repeated if necessary. Green has chloroformed vaccine five hours a day for eight days without diminishing its potency, while emulsions containing as many as 100,000 bacteria per loopful have been made free in one to six hours. Only non-spore-bearing bacteria are killed in this way; but Green points out that among thousands of specimens examined the only spore-

bearing germs in lymph were non-pathogenic. Green reports 48,027 cases vaccinated with chloroform lymph, giving 97.6 per cent. of success, and an insertion success of 91.3 per cent. As he points out, the method has especial value in sudden and urgent demands for lymph and in hot climates. Gaylord and Wheeler have shown that potassium cyanide in 1 to 200 normal solution has a complete bactericidal action without in any way injuring the specific organisms. Further investigations with these and other substances should be carried out.

Glycerinated lymph is generally dispensed in small glass tubes, each containing enough for a single operation. In Europe it is also sold in small bottles, for vaccinating on a large scale. Ingenious modifications consist in putting up glass or ivory points, coated with the lymph, in sealed glass tubes. Dry points are still in use and are preferred by many to the glycerinated lymph. They are sometimes made from glycerinated virus, the drying being assisted by coating or mixing with sterile blood serum. Much glycerinated lymph sold in the United States has been of very poor quality, but there has been a distinct improvement and it should be preferred to the dry vaccine.

The preparations are rarely free from bacteria. The extensive examinations of Rosenau and many others rarely show no growth, but the number may be very small. It seems quite possible to reduce it to less than twenty per preparation. In "poor" vaccine there may be from several thousand to a number too large to count.

Vaccine in all forms, dry or glycerinated, is capable of deterioration from a number of causes. Kept free from bacterial contamination and at a low temperature, the virus remains active for many months. High temperature is likely to weaken or even destroy the activity of the virus. In tropical Africa it is said that humanized vaccine, inoculated arm-to-arm, loses its effects in three or four generations. Animal lymph passing through the Red Sea must be packed in ice.

The question of the relative strength of bovine and humanized virus is not a simple one, because there is no constant standard for either, and the proportion of takes with the two kinds varies greatly. Much humanized virus was almost or quite inert in the days when it was the only kind used. Bovine virus also may become weak. There has been an effort on the part of many makers to furnish the weakest possible vaccine. This is very attractive as long as the question of immunity is not raised, but it goes far to defeat the object of the operation and to give opponents of vaccination arguments against its value. The ideal should be the most intense specific action compatible with a safe local lesion. Much could be done in this way by a scientific application of the known facts of descent and of the increase of virulence of specific germs.

The practical advantages of bovine virus are obvious. It permits selection and cultivation of seed more than does human vaccine. It can be prepared in large quantities, at short notice. It is free from the danger of syphilis, and with proper safeguards can be made as harmless, bacteriologically, as human virus can. The chief disadvantage is the possibility of contamination with pathogenic germs; but this can be wholly avoided by careful examination of material before it is put in the hands of vaccinators.

The Operation.—The first method, and that of Jenner himself, was simply an imitation of the variolous inoculation. Punctures or short incisions

were made and the virus inserted. Later, blisters were raised on the skin and the virus placed on the abraded surface. The incisions were increased in number, then cross scratches were made, and finally the operation became a denudation of the epidermis, sometimes of very considerable extent. The disadvantages and dangers of such an operation are obvious, for while it is possible to abrade so superficially that the vaccine will take and yet the epidermis heal over before the vesicle forms, as usually made the abrasion is followed at once by a scab of more or less thickness, under and around which the lesion must develop. The scab not only interferes with the development of the normal vesicle, but is irritating and induces rubbing or scratching, which promote secondary infection and give the most favorable conditions for the development of infections from germs either previously in the skin or introduced in or with the vaccine. Tetanus especially may be expected to flourish under just such conditions.

The best method would seem to be the simplest; and, in fact, incisions are the only operations permitted by the vaccine laws of Germany and are recommended by the Local Government Board of England.

The point of election for vaccination is the outer surface of the upper arm, over the insertion of the deltoid muscle. This is not only convenient for the operator but also for the patient during the development of the lesion, and it seems less likely to be followed by severe glandular complications than are many other parts. The leg is sometimes vaccinated in order to avoid the disfiguring effect of a vaccine scar. In regard to this it should be said that a normal vaccine scar is not a deformity, and on the other hand any part of the leg is more exposed to traumatism and therefore to complications than is the upper arm. The writer always refuses to vaccinate on the leg unless the patient will stay in bed until the vesicle has healed, an objection that never fails to change the situation. If the leg must be vaccinated, the operation should not be done on the front of the thigh, but on the calf below the head of the fibula. Flachs recommends the side of the chest, about the level of the sixth rib, in the axilla, because it leaves a scar that is not visible, has little motion, and can be easily bandaged. The greater heat and moisture, and hence the greater danger of complications, make this situation most undesirable.

The number of insertions has an important bearing on the probability of taking, as well as on the protection, and we should not depend upon one. The German regulation of 1899 requires at least four incisions each 1 centimeter long and 2 centimeters apart. The Local Government Board of England directs that four vesicles should be produced and that the total area of vesicle formation should be not less than half a square inch. The author's plan is to make not less than two incisions, each about 1 inch long, and from $\frac{3}{4}$ to 1 inch apart; but in case of exposure to smallpox to make three or four, each 1 inch long.

"Vaccination is to be looked on as a surgical operation and carried out with all the precautions necessary for the prevention of septic infectious disease. Especially must the physician carefully consider the cleanliness of his hands, the instruments, and the place of operation" (German requirements of 1899). The seat of the operation must be clean, but not necessarily treated with antiseptics. Usually it is enough to clean the skin with sterilized water, but if the arm and the clothing are dirty the arm must be thoroughly washed with soap and water. Even in such cases it is doubtful

whether antiseptics should be used, but if they are they should be washed off with alcohol and ether. The less the skin is irritated the less the danger of complications.

The best instrument to use is a scalpel, sterilized by dry heat, steam, or boiling. The incisions should not be deep enough to draw blood in large drops. Minute drops do no harm. If the incision is too deep it is better to make another. A little practice enables one to estimate the toughness of the skin and the sharpness of the blade, and to get at least the latter part of the incision the proper depth. (Cross scratches and punctures are forbidden in Prussia.)

In the incisions the virus is gently rubbed, *not ground*, and then allowed to dry. Dressings are not necessary in the beginning. Pads, plasters and shields increase irritation by heat and moisture and often cause softening and breaking down. If the clothing is not perfectly clean it is well to pin a piece of sterilized calico on the sleeve so as to protect the seat of operation. Bathing need not be omitted, nor any ordinary occupation avoided. A properly made wound quickly heals. A normal vesicle has a tough skin and cannot easily be broken before it is mature. If the vesicles become broken a light protective dressing, not more than four thicknesses of aseptic gauze, should be put over the wound in such a way as not to rub. Collodion answers well, but should only be applied along the edges of the gauze. If the vesicles become infected they should be treated like other infected wounds, and by no means neglected from fear of ruining the vaccination. It is better to vaccinate a second time than to allow such a wound to go untreated

Clinical Features of Vaccinia in Man.—The best indices of the efficacy of vaccination are the course of the vesicle, the general symptoms, and the scar. Ultimately we may learn more exact guides to the immunizing power of vaccine, but at present we can only say that if the vesicle and scar are characteristic there is more or less immunity; if they are not characteristic we must admit that immunity can not be considered present. The importance of knowing the characteristics of the vaccine lesions, strongly insisted upon by Jenner, is therefore obvious. It is chiefly on account of the great diagnostic value of the vesicle and scar that subcutaneous methods of vaccination are not to be commended. These quasi-scientific methods reach their extreme in the proposal of Joukowsky to vaccinate the umbilical cord.

The typical features of vaccinia are singularly alike in successful cases. The stage of incubation lasts about three days. The seat of inoculation may heal at once, or show a local reaction such as redness or failure of the incision to heal rapidly, depending partly on the condition of the subject, partly on the irritation produced at the operation. At the end of the third day small papules appear. They are rounded but soon become flattened with increasing size, round or oval in outline, of a bright red color, and feel hard but superficial. On the fourth day the summit becomes vesicular, and a central depression or umbilication rapidly develops. By this time the skin around the lesion is deep red and slightly swollen, and this areola or halo grows wider as the lesion becomes mature. By the end of the seventh day the vesicle has reached its full size. It is round or oval, flattened on top, the middle part umbilicated, and sometimes shows a small scab from the incision. The top is whitish, yellowish, bluish, or grayish, sometimes compared with

pearl or alabaster. The sides are sloping; the skin close to the base is deep red, extending from 1 to 2 centimeters; and beyond this, sometimes, there is a paler zone which passes gradually or abruptly into the healthy skin. The contents of the vesicle are clear and watery but somewhat sticky. If punctured the vesicle may be shown to be multilocular. By the eighth day the vesicle looks yellowish; the middle part is sometimes fuller for a short time, but in a day or two sinks down, from desiccation ("secondary umbilication"). The areola is often redder at this time, 2 to 3 centimeters or more in radius; the surface is rough, like orange peel; the edge is often sharply circumscribed. This part is indurated, sometimes quite deeply. Its outline may be very irregular, with islands of red skin near the edge. In such cases the arm is swollen, the skin feels hot, the axillary glands are swollen and tender. From the ninth day the areola fades, sometimes becoming yellowish from altered blood; the swelling subsides. From the eleventh or twelfth days the vesicle rapidly dries, forming the "scab," which is brown, hard, and wrinkled or fissured. Finally, sometimes not until the end of the third or fourth week, the scab falls off, after becoming loose at the periphery. The scar at first is deep; the edges are sharply defined; the floor flat, and deep red in color. It slowly grows pale and nearer the level of the skin, and shows distinct pits or "foveations," one of the most important features of a "good" vaccination. The final size of the scar is much less than that of the recent state or the mature vesicle.

The local sensations associated with the development of the vesicle vary much in different individuals. Some do not complain and show no evidence of rubbing or scratching. Others, who do not seem more severely affected, complain bitterly, and cannot be prevented from rubbing, scratching, or tearing at the skin. During the height of the development of the vesicle the patient often, but not always, experiences more or less malaise, loss of appetite, sometimes nausea or even vomiting, headache, and pain in muscles and bones or in the lumbar region.

As regards the body temperature Hennig and Bohn found a slight rise—0.5° to 0.7° F. in the first three days; but Sobotka could not. If present it is doubtless due to irritation of the wound. From the third to the seventh day the temperature is remittent, rising a few degrees, and remains about this point but with less marked remissions for two or three days longer, and then rapidly falls to normal. The fever does not seem to bear any proportion to the size and number of the lesions, provided they are not complicated, but is closely related to the areola, according to Bohn. Severe nervous symptoms, especially convulsions, do not occur. Huguenin looks upon fever as an essential part of vaccinia, as Zaehrer (1846) did long before. According to him children who do not have fever must be vaccinated again, but Sobotka in a few cases could find no definite elevation of temperature in the vaccinated new-born. Vaccination after a take does not alter the characteristic curve, nor does opening the vesicle (Sobotka). The nitrogen excretion is increased for a short time about the tenth day, and diminished later.

The red blood corpuscles and hæmoglobin show no distinct anomalies in vaccination, but the leukocytes, according to several observers, are increased. In primary vaccination Sobotka and Enriquez and Siccard found a leukocytosis of as much as 23,000, the former with the polynuclears, the latter with the mononuclear cells increased; myelocytes were rarely present. Billings found a maximum count of 15,000 leukocytes, with the neutrophiles

PLATE XII

FIG. 1

Fifth Day.

FIG. 2

Seventh Day.

FIG. 3

Twelfth Day.

especially concerned, most marked from the sixth to the eighth day, and disappearing in two to four days more. Sobokta also found an early leukopenia, and a secondary leukocytosis, beginning about the tenth day, with an intermediate low leukocyte count. Courmont and Montagnard saw nothing abnormal in the blood in adults, and Enriquez and Siccard found the blood negative in generalized vaccinia. Sobotka calls attention to the resemblance of the blood changes to those in variola.

The Nature of the Changes in the Body after Vaccination.—Our knowledge of the processes brought about by vaccination is not as complete as it is in the case of several other infectious diseases. We can no longer look upon vaccination as merely a local skin lesion, but the difficulty of recognizing the parasites and the doubt surrounding inoculation experiments throw much uncertainty about the further details of the pathology. It was supposed at an early time (Reiter, 1872) that the parasites of vaccinia occur in the blood, but later investigations were contradictory. Raynaud (1877) was not able to vaccinate with blood from vaccinated children, even taken from near the vesicle. Monti found the heart-blood non-infectious. He, and also Guarnieri, found the supposed parasites in the lesions in the larynx and pharynx, and Monti showed that the latter were infectious, as were also the lungs, testes, and spinal cord, while the other organs were non-infectious. This negative result was opposed by Frosch (1896), who claimed that vesicles could be produced by inoculation with almost all the organs, the inguinal glands and spleen being most certain, and that this continued for three or four weeks after vaccination. These investigations indicate, as pointed out by Huguenin, that it is not the dying out of the parasites that causes recovery from the symptoms, but that the body acquires a new condition, in which the infectious agent is indifferent; or, as it is now expressed, the body is immunized.

That protective substances are formed in vaccinated animals is *a priori* probable, and was demonstrated as early as 1867 by Froelich. The work of Raynaud, however, gave a stimulus to experiments not yet brought to a conclusion though already of great value. There are many apparent contradictions in the results, but the following summary gives the chief additions to our knowledge of the subject:

The blood-serum of vaccinated animals during the maturity of the vesicle or somewhat later—*i. e.*, from the eighth to the fifteenth day—is effective against subsequent vaccination. After that time the serum is not effective in checking wholly or in part the development of vesicles. This power is probably closely associated with a precipitating action.

As shown very early (1892) by Sternberg, and confirmed by Kinyoun, Reed, and others, the serum of immunized animals neutralizes vaccine, and evidently contains a substance that kills or inhibits the specific agent. The substance is produced in very small quantities, so that it can not easily be applied as a practical measure, and soon disappears from the blood, leaving the organism able to check the activity of the parasites and to render their toxins harmless. Under the influence of the parasite the body produces protective substances which are antiparasitic in other bodies. That the parasites are not killed at once, even under the active immunity, is demonstrated by many of the experiments. In the immune body the parasites are able to live for a time; in others, they cannot only live, but also cause infection.

Freyer made clear what some earlier observations had shown to be probable: *viz.*, that repeated injections of vaccine lymph furnish an antivirulent serum of greater power than can be obtained by the ordinary skin inoculation. At present this work has no practical application, but its theoretical bearing is very important, and modifications of the previous experiments may open up new therapeutic possibilities.

Empirical Facts Regarding the Immunity of Vaccinia.—Vaccination produces immunity toward itself at a somewhat variable period. When vaccination is repeated daily, as in the "vaccinization" sometimes used, it ceases to take usually between the fourth and sixth days. By the eighth day in a normal vaccination there is immunity not only to vaccination, but also to smallpox. Exceptions to this made Layet put the period of safety at the ninth day, and Burckhardt the eleventh. Most of the experience regarding the exact period of immunity against smallpox is derived from the early days, when the results were tested by variolation. Sacco got only local eruptions by inoculating smallpox from the eighth to the eleventh day; none at all after that.

It is irrational, however, to fix a definite time for the appearance of vaccine immunity. As in other diseases this varies within certain limits, according to the subject and the intensity of action of the vaccine.

A very important practical question is with reference to insusceptibility to vaccination, regarding which there has been much unnecessary difference of opinion. It was known in the period when smallpox was universally prevalent that certain people escaped it. The conditions can hardly be essentially different in vaccination. It is not to be supposed in either case that the immunity is permanent and complete. Illoway has published a case suggesting that one part of the body may be immune and others not, toward vaccination. If we admit, as some do, that there is no such thing as natural immunity against vaccination, we have to ascribe all the failures to imperfections in the lymph or technique; and from a practical standpoint we cannot do better than take such ground. The alternative is scientifically well founded, but can not be positively proved. Few can say, with Cory, that they have made many thousands of vaccinations without a failure, unless the criterion of success is placed dangerously low; but many can recall cases in which several unsuccessful attempts have been made, and then at some later time the patient has taken vaccination or acquired smallpox.

Smallpox itself does not render the body permanently immune to vaccination as is proved by numerous cases. It is often assumed that if vaccination takes, the subject would have taken smallpox if exposed; on the other hand, if it does not take the subject is supposed to be immune. Neither conclusion is justified, and the second one has often led to serious consequences.

Congenital or Hereditary Immunity.—Curiously in contrast with the disbelief in temporary insusceptibility to vaccination is the view that has been expressed as to inherited immunity from vaccination of the mothers. There are several sides to this question. In the first place it may be said that vaccination has not been general enough nor perfect enough to account for a large number of immune children. There are doubtless cases of congenital immunity to smallpox, from intra-uterine infection; but these are too rare to permit any other conclusions than that vaccination in the late stages of pregnancy may give immunity to the fœtus. The most important aspect of

the question is that no convincing investigations have been published demonstrating the alleged immunity on a large scale. Huguenin gives some interesting data. Thus, Perroud vaccinated a pregnant woman and failed repeatedly to vaccinate the child. Gast vaccinated sixteen pregnant women and was able to vaccinate all the infants two or three days after birth. The pustules showed only slight redness, but Gast asserts that is often the case in the new-born. Burckhardt vaccinated eight infants whose mothers had been vaccinated in the eighth or ninth month, with results almost wholly negative. This was true of some other experimenters; but on the other hand Kranz and Wolff (each seventeen cases, none immune) and others got positive results in some or all cases tested. While Lop thought 70 per cent. of such children were immune, Hervieux considered the immunity so produced exceptional. As no evidence has been advanced showing the duration of immunity acquired in this way there is no reason to depend upon it in practice.

Vaccine immunity can probably be acquired, as that of variola is thought to be, through milk; but very little is known on the subject, the scientific interest of which is great.

As vaccine immunity varies in the time of its appearance, so does it vary in duration when once established. This general law, true of all diseases that produce immunity, was often unrecognized in the early days of vaccination, and even now is often overlooked. Failure to recognize it lies at the basis of much of the present-day smallpox, and much of the anti-vaccination movement. Even in Jenner's time there were those who doubted life-long immunity, some of them putting the time as low as three years. Early cases of smallpox in vaccinated people and early revaccinations were misunderstood, and it was not until revaccination was carried out on a large scale that materials were prepared for such a demonstration as that of 1870–1871.

Since revaccination is an essential part of the operation it is necessary to learn something about its operation, and Bohn gives a useful classification of the results of this in practice:

1. Completely successful. Lesions precisely like those in primary vaccination; all the phenomena severe. Incubation three days, traumatic reaction; rapid formation of papules and vesicles; marked areola; typical pustule at the end of the seventh day. Fever on the fourth day; pain and swelling of the axillary glands on the sixth day; induration of the areola on the seventh and eighth days, with swelling of the upper arm; end of fever at the tenth or eleventh day, after going as high as 104° F.

2. Like the first class, but with a more rapid course. Height of the pustular stage on sixth day; fever from the fifth to the eighth day; slight glandular swelling.

Both of these classes furnish active lymph on the fifth and sixth days.

3. Short incubations, twenty-four to thirty hours; at the end of this an itching papule; vesicle on the fourth day, with or without umbilication; pain in the axilla. On the fifth day a brief appearance of areola, with very little fever. By the eighth day desiccation. From this and the forms to be described vaccination cannot be carried out.

4. Rapid development of an abortive lesion with minute vesicle on the second and third day; very small areola. This group cannot be sharply separated from—

5. In which there is either no reaction, or only a slight erythema.

These incomplete lesions have an important but still unsettled bearing on the completeness of immunity. They often result from and indicate imperfect immunity, and the partial success may be said to increase the immunity. But how long this is going to last in an individual patient we cannot tell. Such patients, in times of danger, should be revaccinated.

It is clear that no fixed period can be given for the duration of vaccine protection. The ten-year average is probably too long for the individual, but gives good results when followed on a large scale; the periods of three months or one year advocated by certain vaccinators is shorter than is necessary for practically complete protection; the five-year interval of Japan is a good one in many respects, though perhaps not better than the revaccination in the twelfth year obligatory in Germany. The success of revaccination varies much in different times and places, a large part of the variation being obviously due to perfection of technique and quality of lymph. In Germany it often exceeds 90 per cent., and in any place where the primary vaccination is good it is usually more than 50 per cent.

Vaccinated people may acquire smallpox, but in much smaller proportion than unvaccinated. This has been shown so often that it is remarkable that those who oppose vaccination because of its occasional failures do not recognize it. The general superiority of the revaccinated German soldiers over the civil population in 1870–71 has been mentioned. This becomes more obvious by comparing some figures.

The mortality	in	the army	was	3.53	per	10,000.
" "	in	Dresden	"	32.66	"	"
" "	in	Berlin	"	63.26	"	"
" "	in	Hamburg	"	107.5	"	"

The total statistics for Germany are most convincing, but a few examples must suffice. According to the reports of the Imperial Health Office there were, among the 56,000,000 German population in the thirteen years, 1891 to 1903, only 626 deaths from smallpox. In Berlin there were 70 cases (not deaths) in seven years, in Cologne 1 in ten years, and in Frankfort 9 deaths in ten years. The cases are most frequently in foreigners, and the cities most affected are those chiefly resorted to by foreigners. Thus, 5 fatal cases in Berlin in seven years were all in foreigners. Another striking example is furnished by the exposure of 260 medical students to 2 patients with smallpox. Two of the students contracted smallpox, both of them Italians (and both revaccinated).

Another well demonstrated fact is that vaccinated people who contract smallpox have it, on the average, much less severely than others. Huguenin, from the statistics of 62 hospitals, gives the following: Mortality of unvaccinated from smallpox, 46.6 per cent., of vaccinated, 9.2 per cent. These figures do not apply to other statistics, as both the type of epidemic and the efficacy of the vaccination vary. Spalding states that no vaccinated schoolchild in Chicago has had smallpox in the last ten years, though the disease has existed in epidemic form part of the time. Of 600 students who visited the smallpox hospital frequently, none took the disease. All of them were vaccinated and revaccinated.

Abnormalities of Vaccination.—Vaccination does not always run the typical course (even in primary cases) that has been described. Jenner well

understood this and pleaded for a careful training on the part of vaccinators; but this has often been neglected, with disastrous results in many cases. The variations are numerous, but can be placed under a few simple heads, as in the classification of Colcott Fox, modified by Pernet: 1. Local abnormalities or irregularities in the development of the vesicle. 2. Incidental exanthematic eruptions. 3. Diseases inoculated with lymph at the time of operation. 4. Diseases chiefly septic, which find a nidus in the wounds subsequent to the operation. 5. Diseases excited in subjects specially predisposed to the same. 6. Accidental vaccination. 7. Intercurrent disease.

The local lesion may be atypical either in its physical characteristics or in the time of its evolution. Differences in the time and duration of the various stages are common in revaccination, and have been described in connection with that. In primary vaccinia they are not so usual, but may occur either from partial immunity or from inferior lymph. Rapid beginning sometimes occurs, and is likely to be followed by an abortive later course. Poor lymph often causes slow development of the vesicle, which may not appear for from several days to several weeks, or even months, as claimed by some authors—one year in a case reported by George Harley; fourteen years by Sir Thomas Watson. A delay of more than three or four days should stamp the operation as imperfect, unless a typical lesion follows. In that case the event should be recorded. Sometimes if a second operation is done before the appearance of the papule, both inoculations develop simultaneously, or the one overtakes the other and they reach maturity at the same time. This phenomenon, known since the early days of vaccination, has never been explained.

Certain accidental causes have some bearing on the rate of development of vaccination. Cold retards it; warm weather often hastens it; existing diseases often delay it.

The anomalies of the local lesion may resemble those described as occurring under revaccination, but there are some others that are more certainly due to peculiarities of the lymph. They have long been known as "spurious" or "pseudovaccinia," "vaccinoid," "vaccinella." These have so great a variety that it is difficult to classify them; but if we bear in mind the numerous transitions, the classification of Morrow is very helpful. He described:

1. "A vesicle containing opaque or straw-colored lymph, which makes its appearance usually on the second day; is irregular in form; the areola may be complete by the fourth, fifth, or sixth day. There is nothing fixed or definite in its course; it suppurates; dries up; the scab usually falls off by the tenth day, leaving a pigmented base.

2. "A small reddish tubercle, more sensible to the eye than the touch; enlarges to fourth or fifth day; crusts over; dries up and disappears, leaving no cicatrix.

3. "A single bulla, or instead a group of herpetic vesicles, ('water pocks,' or 'vaccinæ bullosæ,' or 'pemphigoides,') containing transparent fluid, developed from a non-infiltrated base, with thin, tense walls which soon burst. The exuded fluid may give rise to eczematous or phlyctenular eruptions.

4. "A vesicle which may run a normal course until the eighth or ninth day, then rupture, crust over, with progressive ulceration beneath. The ulceration may extend both superficially and deep. There is usually pain and swelling of the axillary glands, and a high degree of constitutional disturbance.

5. "A pigmented tubercle..supposed to be a specific product of bovine lymph, as its appearance dates from the introduction and general use of animal vaccination in this country; it is known as the 'raspberry sore.' It attains the dimensions of a large pea or coffee-grain; globular or irregular; of apple-jelly hue, or from a bright to a dusky red. It is soft and elastic, and gives a deceptive indication of fluid. Puncture is followed by the escape of a drop of reddish serum, the inoculation of which, according to some observers, produces a lesion of identical character. In from four to eight weeks it gradually disappears, leaving pigmentation but no cicatrix." As Morrow pointed out, this is probably not a new sore due to bovine lymph. It seems, in fact, unnecessary to separate this from the second group, of which it seems to be merely an exaggerated example.

The explanation of these anomalies is impossible at present. They probably depend wholly upon imperfections or contaminations, or both, of the virus. There is no convincing reason for looking upon them as indicating protection against smallpox. The writer has seen several cases of smallpox in the last few years with histories and sometimes recent scars of these anomalous sores. Neither is there any reason to believe that these sores are related to vaccinia as varioloid is to smallpox. In some cases there is a short immunity to vaccinia, and sometimes (hard to prove), apparently to smallpox; but neither are constant. They are related to "vaccinia without eruption." This may be admitted as a theoretical possibility, but it has no practical value.

In all cases where the vaccine lesion is atypical in course or in the scar it leaves, the operation should be repeated within a period depending largely on the danger of smallpox. If that is present, it is better to vaccinate at once; if not, within six months or a year at most.

An interesting but unimportant anomaly is the appearance of small vesicles near the principal ones about the third or fourth day—secondary vesicles, or "vaccinolæ." The writer is convinced they are not always due to accidental inoculation of the surface of the skin, but that they arise from germs transported in the skin but not necessarily specific germs. They are not uncommon in vaccinated calves, and though they recall the distant eruption in natural or inoculated smallpox, they are probably quite different in cause and significance. They do not necessarily indicate a strong or active specific germ, but in calves often follow inferior lymph.

Incidental eruptions have been noted from the beginning of vaccination. They depend upon the same general causes as other similar skin manifestations, and require a certain bodily predisposition. They have various types —roseolar, resembling the rashes of measles or German measles, or more diffuse like that of scarlet fever; or they are urticarial or like the various manifestations of erythema multiforme. Most of them begin near the seat of inoculation, but the erythematous form has a special predilection for the extremities, and the urticarial variety may involve the mucous membranes, as the bronchi. These two forms may begin as early as the second day; the more superficial eruptions usually late, from the seventh to the tenth. Minute vesicles sometimes occur at the height of the rash, and pigmentation with degeneration follows.

Relapse of vaccinia has been reported by a few writers within a month or six weeks of the operation.

An anomaly of some importance is the hypertrophied scar that sometimes follows. It may occur even after a typical and uncomplicated lesion. Red at first, it finally becomes pale. It is rather hard, involves the true skin, resembles a keloid in appearance, but usually disappears very slowly, and thus is free from the most important characteristic of true keloid, which, however, sometimes occurs in the negro.

In some cases a growth of hair is stimulated around the scar.

Generalized vaccinia is a term that has been applied to conditions not always the same. Strictly speaking it should be applied to cases in which a widespread eruption appears on the body, with the anatomical and infectious characters (inoculability) of the primary vesicle. Most of the cases reported under this name have been eczema or other skin disease in which vesicles or pustules have occurred in larger or smaller numbers. In some it could be demonstrated that multiple infection had occurred from scratching. In many the lesions were not characteristic in course, though they were in anatomical features. Henoch has emphasized the close anatomical resemblance of certain eczematous and accidental eruptions to vaccinia and variola. In a few cases there was a widespread infection without a previous skin disease. Martin reported one in which a calf was successfully inoculated from the contents of some of the vesicles, and from the calf in turn a number of children and an adult. Groth reports a case and states that from 1885 to 1900, out of 2,285,579 vaccinations in Bavaria there were 50 to 60 cases of generalized vaccination. As Malcolm Morris says, the remarkable thing about generalized vaccinia is that it is not more frequent. The prognosis is good in simple cases; bad in those depending upon an eczema.

Accidental vaccination and auto-vaccination are not very uncommon. They are likely to occur from scratching of the vesicle, though they have often been produced by infection from one person to another. In many cases the genitals have been the seat of the secondary vesicles, often producing, especially on the vulva, lesions that may give rise to much difficulty in diagnosis. The same difficulty often arises when the vesicle is in other parts of the body. Another common seat of accidental vaccination is the face. Mucous membranes in various localities have been involved. A common and very important locality is the eye, either in the conjunctiva or the cornea, and which was fatal in a case reported by Dietter. Blindness has often followed, and in 9 out of 61 cases there was more or less disturbance of vision.

Accidental vaccination of the nose is perhaps more frequent than the reports indicate. Lublinski gives 4 cases, 1 original. An interesting location was the tongue, in a mother who sucked the virus from her child's arm. Physicians have inoculated their lips by blowing through vaccine tubes. The ease with which infection can take place is shown by a case in which a physician who dressed a child's arm infected the mother by a local examination. An important contribution to the subject is that of the zoölogist Blochmann[1] whose own child was severely injured by vaccination.

The Complications of Vaccination.—The complications of vaccination may be considered with reference to their mode of origin or to their anatomi-

[1] "Ist die Schutzpockenimpfunge mit allen notwendigen Kautelen umgeben?" *Tübingen*, 1904.

cal or clinical peculiarities. Inasmuch as the same sort of lesion may arise either from infection with the vaccine or later, it is more convenient to follow an anatomical-clinical classification.

Vaccinal ulcers may resemble the anomalous ulcerating form previously described, but differ in that they may occur after the vesicle has made a typical beginning. They are especially likely to occur when poor virus is used, but may follow good vesicles which have become infected. Anæmia and cachectic conditions are predisposing causes. The ulcers are indolent, with flabby and sometimes exuberant granulations. Glandular complications are not always present. Extensive loss of tissue may follow, with large and deformed scars. If the complication comes on after the vesicle has reached maturity, some protection is probably given, but unless the operator is satisfied as to the course, the vaccination should be considered a failure. A number of deaths have followed this complication.

Post-vaccinal gangrene can not be sharply separated from the preceding, but there is another form of gangrene, called vaccinia gangrenosa by Hutchinson, in which multiple eruptions occurred on the eighth day, surrounded by an areola, in which gangrene developed, with death in the second week. In a case of Stokes, purple-black spots appeared within forty-eight hours after vaccination and later became gangrenous; recovery followed. Such cases appear to be much less frequent now than formerly. It is probable that in some cases scurvy was present, or some purpuric affection. The condition has been compared with gangrenous varicella.

Hemorrhagic diathesis sometimes first shows itself after vaccination. There may be fatal hemorrhage from the incision. Similar hemorrhages have been observed after vaccination in leukæmia. In all hemorrhagic cases the prognosis is serious.

The most important infectious complications of vaccinia are the *pyogenic diseases*, including *erysipelas*. These are much less frequent than when humanized lymph was used and when instruments were never cleaned. Erysipelas may occur at any stage of vaccination, and is spoken of as early or late, according to the period. It sometimes occurs so early that we must look upon the operation or the lymph as the exciting cause. In most cases it occurs in the second week. The areola is evidently an erysipelatous lesion, but its relationship has not been sufficiently worked out. In most cases there is a distinct history of rubbing or scratching and obvious uncleanness. The disease has occurred in epidemics, due to some fault in lymph or operation, at other times with epidemic erysipelas of other parts of the body. The latter possibility is ground for an important objection to hurried vaccination during epidemics, which often occur at a season favorable for erysipelas, instead of formal vaccination at a more favorable time of year.

The local and general phenomena are those common to erysipelas in any part of the body. The prognosis depends upon the condition of the patient, and the severity and extent of the erysipelas. Unless the complication comes on very late the vaccine vesicle is checked in its development and immunity is not produced. In any case the lesion is infected, ulcerates, and an atypical scar is the result.

Abscess, *furuncles*, *lymphangitis*, *cellulitis*, and *phlebitis*, suppuration of axillary glands, and *pyæmia*, are rare but serious complications that need no special description. *Suppurative parotitis* is a rare occurrence after vaccination. In all the pyogenic complications it is important to treat the

conditions according to the general and special rules that apply to such diseases in any part of the body, and never to neglect or even temporize with them in the belief that the vaccination may suffer. This must be considered a failure in all cases in which the vaccine lesion is involved early, or where its course is altered.

An interesting and important complication is *contagious impetigo*, which sometimes occurs in recently vaccinated people as it does in others. "When due to the vaccine, the cases develop in groups. The vaccine vesicles become pustular, itch severely, rupture early, and infect the body in many places." Voigt mentions a small epidemic following arm-to-arm vaccination from a healthy child, on the eight day. In many cases the infection is accidental. *Pemphigus* is a much rarer complication, sometimes difficult to distinguish from impetigo.

Eczema, psoriasis, and various other chronic skin diseases, sometimes follow vaccination, especially when the operation is done in hot weather. In the majority the skin diseases are already present, not noticed or not brought to the attention of the physician, and then any increase in severity is ascribed to the operation. In all vaccinating the physician should ascertain the existence of a skin disease and either not vaccinate at all, or, in case of danger of smallpox, try to vaccinate in sound skin. In such cases a light but efficient bandage may be used.

Herpes circinatus is a rare occurrence after vaccination, explained by infection with Trichophyton tonsurans, a common parasite of cattle.

Measles, scarlet fever, and other acute exanthemata, sometimes occur in the course of vaccinia without causing any serious effect on each other. Jenner noticed that both measles and scarlet fever caused a suppression of the areola, which reappeared after the other exanthem faded.

Simultaneous Vaccinia and Variola.—It was early observed that smallpox and vaccinia could exist at the same time in the body, and though some assert that in such cases the variola is modified, others say, and more accurately, that the severity of the smallpox depends partly on the period at which the vaccinia is introduced. Considering the close relationship of the two diseases, it is easy to understand that they can develop together, and that the immunity of one will check the growth of the other. The situation is not unlike that which exists when vaccine is inoculated on successive days. All the lesions may develop together until immunity is set up by the earliest, and then all subside.

Huguenin describes the chief possibilities with smallpox as follows:

1. In case vaccine is inoculated just before or during the primary fever of smallpox the latter proceeds uninfluenced, unless there has been a previous vaccination. The vaccine, however, fails because of the immunization of the body by the variola.

2. If the vaccination is made at the end of the stage of incubation of variola, both infections may go on side by side.

3. If the vaccination is made in the middle of the incubation of variola, the eruption of the former will occur two or three days before the primary fever of the variola. Only a mild smallpox or a varioloid develops.

4. If the vaccination is made in the beginning of the incubation stage of variola, the difference being six to eight days, the variola will be abortive.

5. In the first day of the incubation, vaccination prevents the smallpox, though there may be fever.

6. If a child in an infected house is vaccinated before it is infected, there will be no symptoms of smallpox.

There are, however, some exceptions. The variola may proceed unaffected by vaccination, which may not develop until after the smallpox has run its course. Or vaccine and smallpox may occur simultaneously, the latter retarded but not rendered abortive. Or the vaccination may develop imperfectly and the variola run its course and even reach a fatal end. In view of the great number of more favorable cases, such accidents should not prevent vaccination in every case where infection is threatened. In the first three days after infection, even in the fourth or fifth, careful vaccination should be made in at least four places. In such cases, too, especially if the type of variola is severe, one may with advantage practice successive vaccination every day until the eruption becomes vesicular.

The importance of good vaccine is shown by the facts just set forth, and was illustrated by a patient seen with T. B. Cooley, Health Officer of Ann Arbor. The patient was vaccinated on account of exposure to smallpox but did not take. About a week later he was again vaccinated, but the vesicle did not appear until December 6, the eighth day. He had been exposed to smallpox up to November 28. Symptoms began December 6 and the eruption December 8. When seen by the author he had a few resolving papules on the face and body, and one on one hand. There were two fairly good vaccinia vesicles with a fading areola. The epidemic was a very mild one, but in this patient both smallpox and vaccination seemed to have been cut shorter than usual.

Syphilis is not to be considered as a possible complication if bovine lymph is used, except from extraordinary carelessness on the part of the operator or the patient. The same may be said of *leprosy*, which has in rare instances followed arm-to-arm vaccination in leprous regions. Leprosy bacilli have been found in the lymph of vaccine vesicles in lepers (Arning and others). *Tuberculosis* also has only historic interest in connection with vaccine, though it will always be important for propagators of vaccine. Vaccination sometimes seems to accelerate the course of tuberculosis.

Tetanus has a remarkable history in connection with vaccination. It is so rare in general that only 7 cases could be found in the Index Catalogue, and McFarland could find only 15 altogether in the literature up to 1899; yet he was able to collect 52 cases reported more or less completely, and to learn of 28 more not well authenticated, after that date. Since then a few more cases have been reported. McFarland found from a careful study that: 1. Tetanus is not a frequent complication of vaccination. 2. The cases occur in small numbers after the use of various viruses. 3. An overwhelming proportion occurred after the use of a particular virus. 4. Tetanus bacilli may be present in virus in small numbers, derived from manure and hay. 5. Through carelessness or accident the number may be greater than usual. 6. Avoidance of the complication is to be sought in greater care in the preparation of the virus.

Willson (1902) first found tetanus bacilli in vaccine virus, and Carini out of 400 examinations of 50 different specimens of lymph, found tetanus bacilli 5 times. He concludes that they belong to the normal flora of lymph, but occur rarely and in small numbers, because in a series of specimens of the same lymph he found the germs in only 1 tube. Glycerin is a poor protection against tetanus germs, as Rosenau has shown. No com-

plications came under Carini's notice from the lymph examined, though thousands of preparations had been used. As preventives of tetanus he advises superficial incisions, no bandages, and careful examination for tetanus germs in vaccine.

Reading the accounts of separate cases, and still more those of epidemics of complications, gives one an unfavorable view of vaccination. Three things must be considered in this connection. We no longer, thanks to vaccination, see or suffer the horrors of pre-Jennerian smallpox with its complications. Nothing else would have removed these so effectually as has vaccination. In the second place, many of the accidents—almost all of the severe ones—are avoidable. Moreover, we need to take a broad survey of vaccination in order to get the real proportions. This has been admirably done for us by Voigt, for thirty years director of the Hamburg Vaccine Institute, having probably the largest vaccine territory in existence. In this time 400,000 persons were vaccinated in the institute; in the whole district, nearly 600,000 in twenty years. Out of 589,586 school-children vaccinated and revaccinated there were: Inflammatory complications, probably chiefly due to staphylococci, 35; 2 fatal. Erysipelas, 13; 2 fatal. Phlegmon, 4; 2 fatal. None of the pyogenic cases were due to the operation itself. Eczema 293, 85 of which began before the vaccination. Urticaria, 32 cases. Impetigo, 85 cases, 50 of which were not due to vaccination. Tetanus, 1 case, recovered; this began on the fourth day, several days after the patient had fallen upon his head.

Another useful series of data is the following[1]: In Germany in thirteen years, 1885–97, 32,166,619 children were vaccinated; 115 of them died within a few weeks or months after the operation, from injuries presumably due thereto. This gives a mortality of 3.5 per million. In 67 cases only, however, was it probable the injuries were due to vaccination. In 1902 there were no deaths traceable to vaccination, but 2 from subsequent invasions. As the report says, *compulsory school attendance is far more dangerous than compulsory vaccination.*

At various times vaccination has been thought to have a curative effect upon other diseases. Most of them are diseases in which it would be difficult to prove the exact relations, such as whooping-cough, leprosy (Rake), tuberculosis (Winogradoff), and various skin diseases. Hypertrophic scars, such as sometimes follow vaccination, and nævi, seem more promising. In such cases superficial scarification and vaccination with lymph of good quality would seem justifiable.

The Practical Application of Vaccination.—There is a remarkable discrepancy between our knowledge of vaccination and its benefits, and the practical application of this knowledge for the prevention of smallpox. Errors of technique and exaggerated ideas of vaccine immunity have been partly responsible for the neglect of and opposition to vaccination; but, though we still need further information concerning many details, we have enough to warrant a much wider use of vaccine than now exists in many countries. It is certain that vaccination applied to the fullest extent, and repeated once or twice in the age of greatest predisposition, has almost abolished smallpox whenever it has been tried. Nothing else has done this, and the experience of every locality that has tried to get along without

[1] *British Medical Journal*, April 16, 1904; p. 903.

vaccination, depending upon sanitation alone, shows that until our ideas of smallpox are radically changed we are not likely to get a satisfactory substitute for vaccination.

The continued existence of smallpox, often in epidemic form, makes more obvious the need of improvement; for, even when the disease is mild it causes far more deaths, more alarm, and more suffering than vaccination ever has, and moreover there is no reason to think that the type will remain permanently mild.

It seems expedient to consider some of the reasons for imperfect vaccination and the possible means of improving the condition.

1. There is no order, system or uniformity about the operation. The result of this is that large numbers of people of all ages remain unvaccinated, usually because they know no better. This furnishes so large a proportion of predisposed subjects that smallpox once introduced is sure to obtain a foothold, and in the epidemics that result even some vaccinated people get the disease and some of them die. The proportion of unprotected people varies in different parts. Perhaps the conditions in Michigan are no worse than the average, as the excellence of its Board of Health has long been recognized. Yet among several thousand people examined by the writer within the last ten years with reference to this point, all above the age of childhood, only 60 per cent. have been vaccinated at all, and most of these had unsatisfactory scars. The limitation of a single vaccination and even of revaccination on the one hand, the great danger of smallpox on the other, and the advantages of widespread vaccination, make the subject not one of individual complaisance, but one that should come under the sanitary control of the authorities.

2. Systematic revaccination, an essential part of the process, is even more neglected. Carried out as it should be, it would make still more certain the protective influence of vaccinia, and so lessen the number of possible foci of variola.

3. No sufficient provision is made for the production of safe and trustworthy vaccine virus. Past experience has shown that the private manufacture of vaccine opens the way for a greater degree of carelessness than should be permitted in such an industry. Recently an inspection of establishments for the production of vaccines and analagous preparations has been made under a United States law. The establishments are inspected and the methods of manufacture, construction and administration investigated. Samples of vaccine are examined, and, if there is any reason, the yearly license is revoked or suspended. The value as well as the need of such inspection is best shown by the fact that within a year of the beginning of the work, four establishments were refused licenses, and others were obliged to improve their methods, rebuild laboratories and barns, etc. There was also improvement as regards bacterial contamination of vaccine.

Unfortunately, the tests as to the specific activity of the virus are so far insufficient, and much of the vaccine used is seriously weak. Regular vaccination at fixed periods would add much to the certainty of securing good vaccine, because makers could prepare for the demand, and the virus would not suffer, as it does now, from insufficient ripening or from being kept too long after it is ripe.

4. There is no way of being certain the operation will be well done and the result accurately recorded. In many places local or state laws provide

for compulsory vaccination, but this can be and is evaded in many ways. "Internal" and other fraudulent methods are practiced, and false certificates are given by legally qualified but unprincipled practitioners who object to vaccination. Mothers suck out the virus as soon as the operation is done, and as no inspection of the result is necessary, unfounded security is set up, based upon a fallacious belief of widespread vaccination, inevitably leading to disappointment and to erroneous ideas of the value of vaccination.

All these defects arise in a sense from the imperfections of the laws regarding vaccination, many of which are more or less faulty in theory, many of them dangerously so; and all of them in the provisions for their proper application. A recent decision of the Supreme Court of the United States (*Henning Jacobson v Commonwealth of Massachusetts*, Supreme Court Reporter, April 1, 1905, p. 358) is certain to have a great influence on future cases, and probably on laws made by state legislatures and other bodies. The case in point involved the validity under the Constitution of the United States of certain provisions in the statutes of Massachusetts relating to vaccination. The statute was upheld in every respect. The most interesting is that part of the decision that deals with the idea of personal liberty, which is so commonly supposed to be infringed by laws requiring vaccination, and some other statutes affecting public sanitation. It is shown very clearly that "the liberty secured by the Constitution of the United States . . . does not import an absolute right in each person to be, at all times, and in all circumstances, wholly freed from restraint. . . . Real liberty for all could not exist under the operation of a principle which recognizes the right of each individual person to use his own, whether in respect to his person or his property, regardless of the injury that may be done to others."

But for the best results to follow laws compelling vaccination it is necessary to have the active as well as the passive consent of the people, and it is sometimes said that Americans in general would never submit to compulsory vaccination. The writer thinks this is a serious error, and that the chief difficulty at present is the ignorance of the public as to the desired methods —an ignorance not entirely unconnected with defective laws and still more defective administration. The patience with which, in various parts of the country, the public submits to quarantine, detention, spasmodic and inconclusive vaccination, not to mention the unpunished malpractice of ignorant vaccinators, is the best argument in favor of the view that the population as a whole would welcome any wise and conservative law, based upon such experiences as those of Germany. It is sometimes said that general vaccination would open the way for a series of preventive inoculations for various other infectious diseases, but this is not necessarily so. Whenever it can be shown that any other disease can be protected against as well as smallpox can be by vaccination, and with as little risk, it would obviously be well to take advantage of the discovery.

Before any radical change can be made in our vaccination laws, physicians can do much to bring a better sentiment than exists at present, and also to improve the practice of vaccination. They should encourage vaccination and revaccination in all persons with whom they have professional relations, and do this not at times of epidemics, but as early as the occasion permits. They should advise and select a time when the discomfort

of the operation and the danger of complications is least; that is, in the early summer or early winter, and when there are no epidemics of dangerous contagious diseases, like scarlet fever, measles, diphtheria, croup, whooping-cough, or erysipelas.

Parents should be advised to have children vaccinated between the ages of six months and two years, or earlier in case of danger. Children should also be revaccinated when they begin school, especially the public schools, with the danger from the carelessness of other parents. After that revaccination should be practiced according to local conditions, without a longer interval than ten years until adult age is reached, and particularly when new occupations offer renewed dangers. So, for example, recruits, operatives in manufacturing establishments, and those who work in large stores or offices, should be revaccinated.

Individuals with serious organic or constitutional diseases, with severe skin diseases, especially those that induce scratching, should not be vaccinated unless there is immediate danger, but the reasons and risks should be clearly stated to the patients, parents, or guardians, so that greater precautions may be taken. Revaccination in older people should not be done during the existence of any serious disease, unless there is distinct danger of smallpox. In such cases it should be practiced, and the wounds carefully observed. During menstruation, especially the early part of the period, is not a good time for vaccination. The writer has seen vaccination and revaccination carried out several times in the last few years on most of the patients in a general hospital, and though some painful swellings occurred, there was no serious damage.

Every effort should be made to obtain good material. The operation should be looked upon as an important one, and sufficient time and pains taken to make it as aseptic as possible. The patient should be told of the necessity of noting the result and of treating any untoward symptoms, the accidental nature of which should be made clear. Records should be kept, as well for the information of the patient as for that of the physician. With the greatest care, however, certain risks are present, and so it is unwise for the physician to force the operation upon those who are unwilling, or to give assurances of absolute harmlessness.

CHAPTER XI.

CHICKENPOX.

By WILLIAM T. COUNCILMAN, M. D.

Chickenpox (Latin, varicella; German, Wasserpocken-Windblättern; French, La varicelle; Italian, morviglione) is an acute infectious disease occurring chiefly in children; characterized by slight fever and an eruption of vesicles with clear contents which dry up in three days, leaving a granular scab. The disease is the mildest of all infectious diseases, and without complications is attended with no mortality.

History.—As it required the experience of several centuries before the specific nature of smallpox was recognized, a still longer time elapsed before this was clearly distinguished from chickenpox. According to Gregory, Ingrassias, a Sicilian physician, in a work *On Preternatural Swellings*, published in 1553, gives the first distinct description of chickenpox. Vidius, forty years later, described the disease as a variety of smallpox, giving it the name of variola crystallina. Sydenham makes no mention of it. Heberden, in 1767, described the disease under the name of chickenpox, and gave the points of differentiation from smallpox. He made out the period of incubation as eight or nine days, citing the case of a mother who had the disease eight days after the eruption appeared on her children. The disease was not fully accepted as specific and distinct from smallpox until after the smallpox epidemic in Germany in 1870–73. Hebra always regarded it as a form of smallpox, as did Kaposi and Kassowitz. Hebra applied the term varicella to those cases of smallpox which require fourteen days or less for their completion, the term varioloid to those which terminate in the third or fourth week, and the term variola vera to those which last four weeks or more. Heberden certainly included in his description of chickenpox, cases of modified smallpox. It is this form of smallpox which has always led to confusion between the two diseases.

Etiology.—This is unknown. There is doubt about the essential seat of the disease. There is much evidence to show that the virus is not contained in the vesicles, rapidly dies out, or is not in an inoculable form. The disease is easily communicated but the mode of infection is unknown. The weight of evidence is certainly against transmission by inoculation of the vesicle contents. Bryce, Heim, Vetter, Thomas, Czarkert, Fleishman, Buchmuller, Smith, and others, were unable to produce the disease by inoculation. On the other hand, Steiner's results in two cases which he gives in detail seem to be without question. Recently in an epidemic of the disease which occurred among adults in a native prison in the Philippines, and which was investigated by Tyzzer, numerous inoculations were made without results. Animal inoculations are negative. Both the clear and the clouded vesicle contents were used for inoculation without results.

While chickenpox is preëminently a disease of childhood, no age is exempt. The epidemic described by Tyzzer occurred entirely in adults. Probably the high exemption of adults is due to immunity from a previous attack. While the disease prevails more at certain times, it is rarely present to so great a degree that we are warranted in regarding it as epidemic. In large cities it is constantly present. When it appears in a family it usually extends to all the children. It passes through children asylums in the same way.

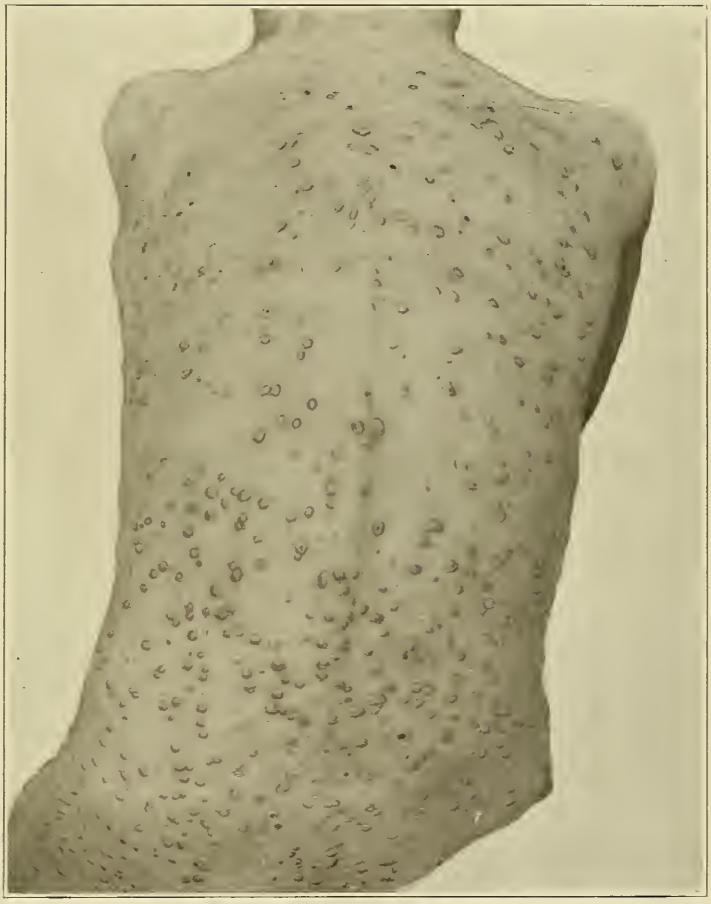
Pathology.—The anatomy of the skin lesions was studied by Tyzzer on vesicles which he excised at various stages. The earliest lesions in the epidermis are found in the areas of erythema which precede the formation of the vesicles. The first change consists in swelling of the cytoplasm and nuclei of the cells. The cytoplasm stains more faintly and becomes distinctly reticulated, the nuclei become distended and the chromatin relatively less in amount. The nuclei usually contain one or several masses of eosin staining material. The areas affected are often very minute, not more than two or three cells being involved. The cells undergo peculiar changes which have been described by Unna as ballooning degeneration. The nucleus of a large swollen cell divides by direct division, and this process is rapidly repeated until a large number of nuclei are produced within the cell. The cells often attain enormous dimensions. The nuclei are usually grouped in the centre of the cell, often so closely packed together that the apposing surfaces are flattened one against the other. Exudation from the vessels beneath the epidermis rapidly takes place and the fluid finds its way into the degenerated epithelium and separates the degenerating cells, forming spaces filled with fluid. The lesion may develop from one or several centres but the various small chambers quickly break into one another, forming a single vesicle. The degenerated epithelial cells do not form the rigid septa which are found in the smallpox lesion. Cells in various stages of degeneration are found free in the vesicle contents or along its floor. The base of the vesicle in which there is an active exudation is almost invariably concave. The vesicles are usually unilocular and not umbilicated, though sweat glands and hair ducts may pass through their middle. Changes are constantly found in the corium; the vessels are dilated and there is proliferation of the endothelial cells of the vessels and of the connective tissue cells. Large multinucleated cells similar to those found in the epidermis may develop from the endothelium of blood- and lymphatic vessels. Later in the process phagocytes may be seen within the vesicle, where they seem to be devouring the remains of the epithelial cells; and they also infiltrate the corium. The fluid within the vesicle contains fibrin, and coagulates spontaneously when removed. The amount of fibrin seems greater after a few days than in the beginning. The vesicles usually rupture. But few polynuclear leukocytes are found, either in the corium or in the vesicle, unless infection by bacteria has occurred. Abortive cases without complete vesicle formation may occur. In these there is a marked localized degeneration of the epithelial cells without any appreciable exudation. These lesions, appearing as reddened, slightly elevated spots, show microscopically a portion of the epidermis wholly necrotic, with the cells disassociated and hyaline in appearance like those in the advanced vesicle. Tyzzer in his description of the lesions has given such a case.

Nuclear inclusions, but without definite form and structure, were described by Tyzzer as constantly found in the affected cells. He found no evidence of multiplication in them. He arrived at no conclusion regarding their

PLATE XIII

Eruption of Chickenpox. The Relative Frequency of the Pocks on the Face and Body is Shown.

PLATE XIV



Eruption of Chickenpox.

nature. So far as the writer knows, there are no records of autopsies in chickenpox so that nothing is known as to presence or character of internal lesions.

It is usual for chickenpox to leave slight cicatrices, which are quite characteristic. They are more frequently seen on the forehead than elsewhere, produce no deformity, and are usually visible only on close examination. They are slightly or not at all depressed, a trifle paler than the surrounding skin, perfectly smooth, and vary in size up to 4 mm. They are due to a very superficial destruction of the corium involving only the papillæ. The destruction is never so deep as to involve sweat glands or hair follicles, hence the cicatrix is never foveated. Rarely there are more extensive cicatrices, usually from infection of the vesicles, with resultant small ulcers.

Incubation.—There is some discrepancy relative to the period of incubation. Gregory says it does not exceed four days and is certainly less than a week. Most observers regard it as longer than smallpox, placing it at fourteen to sixteen days. The period of incubation is without symptoms.

Symptoms.—The character of the onset varies. Usually there is slight febrile disturbance, with headache and nausea a few hours before the eruption appears. In some cases there is decided chilliness. The writer knows of three cases in one family in each of which there was a slight chill at the onset. The temperature is usually low, not more than 100° F. In rare cases it may extend to 102° F. or more. Thomas has observed one case with an initial temperature of 105° F. The temperature usually drops to normal with the establishment of the eruption. If this is very abundant the fever may persist for several days.

The eruption may develop with great rapidity. Welch and Schamberg report a case in which a child was bathed by the nurse and no trace of an eruption was seen. Four hours later there were a number of fully developed vesicles on the trunk. The eruption is preceded by erythematous macules, which are not elevated and may be so slight as to be overlooked. There is no initial induration. In the centre of the macule the vesicle appears. The size of the vesicle bears a relation to the macule and varies from 1 to 8 mm., being usually from 2 to 4 mm. They are usually not round, but slightly oval, the long diameter corresponding to the lines of cleavage of the skin. They project from 1 to 3 mm. above the surface. The edges are sharp. In the beginning they are surrounded by a small erythematous ring, the remains of the original macule. This fades before the vesicle disappears and may be absent from the beginning. The contents are clear and the vesicle appears transparent beneath the thin covering. Before disappearing, the contents become more opaque, but they do not become distinctly purulent without infection. The fluid contains fibrin and coagulates spontaneously when removed. The covering is thin, and vesicles are usually ruptured by the friction of clothing or by the ordinary slight injuries. The vesicles are not umbilicated. Even where a hair passes through the centre it produces no depression (Plates XIII and XIV).

The eruption first appears upon the face and back. Contrary to the eruption of smallpox, the body is more affected than the face and extremities. Vesicles are rare upon the palms and soles, though they do appear. Lesions on the buccal mucous membrane and palate appear, but the vesicles are quickly ruptured and the lesions usually present the form of slight erosions. Vesicles also appear in the vestibule of the vagina and on the prepuce, and

may produce considerable swelling and irritation. Gregory has made the apt comparison of the eruption to that which would be produced by spraying the surface with boiling water. The general duration of the vesicle is three days. They appear in successive crops and the duration of the disease may extend into a week or longer. The vesicles may appear by absorption, in which case there will be a very slight scaly crust formed of the dried epidermis, which is cast off and renewed. They are more frequently ruptured, and a somewhat thicker crust results due to the presence of the dried exudation and the deeper necrosis of the epithelium.

There is practically no constitutional disturbance after the onset. The patient is in nowise ill, though the extensive eruption makes the contact of clothing unpleasant, and there may be considerable itching. There is but little departure from the type of the disease. Thomas mentions a case in which the erythematous macules persisted for thirty-six hours and then disappeared without any formation of vesicles.

Diagnosis.—The only disease with which there is any probability of confounding chickenpox is the abortive form of smallpox, in which the lesions remain in the vesicular stage. The differential diagnosis is given under smallpox. Cases may be found in which at a given period and in the absence of history it is impossible to make the diagnosis. Resort should then be had to microscopic examination of the lesions, or to animal inoculations. The corneal reaction from inoculation is always positive in smallpox and absent in chickenpox. The histology of the skin lesions is different, chickenpox showing the formation of epithelial giant cells which are absent in smallpox; the chickenpox vesicle has a single chamber while that of smallpox is multiple. The epithelial cells in smallpox contain the cytoryctes, which are absent in chickenpox. Even the microscopic examination of the contents of the vesicle at the bedside may be decisive, for the presence in this of the large multinucleated epithelial cells speaks strongly for chickenpox.

Prognosis.—This is invariably favorable without complications, and these are extremely rare, but are easily understood when the pathology of the disease is borne in mind. There are lesions in the skin which can form the atrium of infection for bacteria. Erysipelas may appear, and Holt has mentioned three cases in which it was fatal. Rare cases have been reported in which there was general infection with the streptococcus or staphylococcus, resulting fatally. Disseminated gangrene of the skin may also appear. Synovitis and arthritis have also been seen as complications. None of these conditions are more frequent in chickenpox than they would be found in similar lesions of the skin from whatever cause.

Henoch was the first to show that nephritis may follow chickenpox, and reported four cases, since which others have been noted. The character of the nephritis seems to be the same as in scarlet fever. It is evident that such a complication must seriously affect the prognosis.

Treatment.—There is no specific treatment. Although the disease is so mild, it should not be voluntarily disseminated. Children should be kept from school and isolated during the entire eruption period until the removal of the scabs. Like the other exanthemata, this seems to be the period when the disease is most easily disseminated. It is usually not worth while to attempt to isolate the patient from other children in the family unless there are conditions which would render it unadvisable or dangerous for them to contract it. In such cases complete isolation of patient and attendant may be

successfully carried out. The disease must be considered as among the most contagious, but of the mode of infection we are ignorant. The treatment should be directed solely toward the conditions which the patient presents. Attention should be paid to cleanliness. The hands should be kept clean and the nails cut close, in order to prevent as far as possible infection of the lesions by scratching. The various washes used to allay itching will be found useful. If complications arise they should be treated according to their nature.

CHAPTER XII.

SCARLET FEVER.

By JOHN H. McCOLLOM, M. D.

Synonyms.—Scarlatina; French, la scarlatine; German, Scharlach; Spanish, escarlatina.

Definition.—An acute febrile highly infectious disease characterized by an angina and a general punctate erythema. The types of the disease differ greatly in severity. The intensity of the eruption varies in a marked degree.

History.—Where the disease originated is not known, but descriptions are given of it by medical writers before the Christian Era. In Athens in 439 B. C., as stated by Malfatti, there was an epidemic the description of which, as given by Thucydides, is compatible with that of scarlet fever of a virulent type. It is doubtful if Hippocrates recognized the disease. Aëtius, a Greek physician who flourished about 500 A. D., describes a condition of the skin which resembles that of scarlet fever. Avicenna, who died 1037 A. D., describes an exanthem which very much resembles scarlet fever. To Sydenham must be accorded the credit of giving the name scarlet fever to the disease. He differentiated it from measles. Previous to his time these two diseases had been considered one and the same. In the course of the eighteenth century scarlet fever was studied in all parts of Europe. The authors of that period who published the most important works upon the disease were Navier, Lorry, Sauvage, Desessarts, in France; Storch and Plenciz in Germany; Huxham, Fothergill, and Withering, in England. In Sweden, Norway, Denmark, and Italy many observers described the disease.

In the nineteenth century the disease was carefully studied in all parts of the civilized world, and medical literature contains a vast amount of material on this subject. Scarlet fever is very generally disseminated, although in temperate climes it is much more common than in warm countries. It has been reported as occurring in Iceland and also in Greenland. Scarlatina appeared first in the United States, according to Thomas, in 1735. In 1795 and 1796 an epidemic occurred in Leominster, Massachusetts.

Minor, who carefully studied the geographical position and temperature in reference to the prevalence of scarlet fever, arrives at the following conclusions:

1. "The zone of comparative immunity in the eastern hemisphere extends from 10° south latitude to 20° north latitude.

2. "A zone of comparative immunity in the western hemisphere extends from the equator to 10° north latitude.

3. "Another zone of comparative immunity in the western hemisphere extends from 30° to 35° north latitude.

4. "In times of pandemics occasional epidemics occur at points within the zones of comparative immunity.

5. "When scarlatina epidemics occur within the zones of comparative immunity the disease attacks by preference the Caucasian race.

6. "The outbreak of such epidemics in the zones marked first and second can always be accounted for by the arrival of ships having the disease aboard. Scarlatina can, then, be said to be imported within those zones and, having exhausted itself on the European settlers, the disease fails to become acclimated, and dies out completely for long intervals of time.

7. "In the zone marked third the disease almost always exists in a sporadic form; it only becomes epidemic when it is pandemic in the higher latitudes."

In 1829 and 1830 W. H. Cock[1] reported an outbreak of scarlet fever in the island of St. Bartholomew, and called attention to the fact that there were quite a number of cases of sore throat without an eruption, which he diagnosed as scarlet fever. He also alludes to the peculiar appearance of the papillæ of the tongue as an important aid in diagnosis. This paper is of great interest because he appreciated the fact that scarlet fever may be of an exceptionally mild type and yet give rise to other cases of the malignant variety. The origin of these cases in the island of St. Bartholomew was not definitely shown, but it was believed by Cock that the disease was imported from the United States by children who had scarlet fever on shipboard before arrival at the island. As confirmatory evidence, it is worthy of notice that these children, after remaining a short time at St. Bartholomew, went to Montserrat and soon after there was an outbreak of scarlet fever on this island. Previous to this time scarlet fever was unknown in this locality. In England and Germany the disease is always endemic and frequently epidemic. In the northern part of the United States scarlet fever is much more prevalent than in the southern portions. In the northern states it has been noticed that about once in every five or six years there is quite a general epidemic of this disease which frequently assumes a malignant type.

In the state of Massachusetts the death-rate of scarlet fever per 10,000 of the population in five-year periods from 1866 is as follows:

Years.	*Deaths.*	*Death-rate.*
1866–1870	4,670	6.8
1871–1875	6,782	8.6
1876–1880	3,517	4.1
1881–1885	2,504	2.7
1886–1890	1,810	1.7
1891–1895	2,857	2.4
1896–1900	1,358	1.0
1901	385	1.3
1902	313	1.1
1903	510	1.7

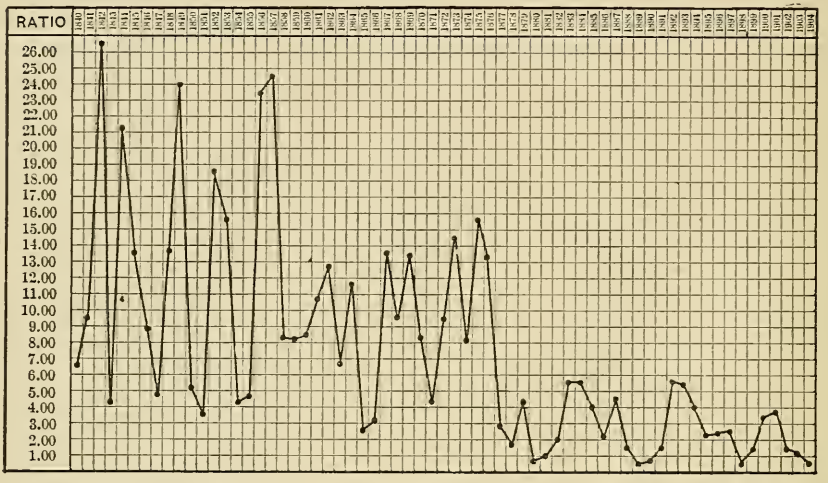
In Boston scarlet fever has always been prevalent, but in the past few years the ratio of mortality per 10,000 of the population has diminished very materially.

Fig. 30 shows the ratio of mortality of scarlet fever per 10,000 of the population in Boston for sixty-five years, 1840 to 1904, inclusive. It will be seen that previous to 1876 the average ratio of mortality was 11.22, while from 1877 to 1904 it was 2.61 Previous to 1877 there was a marked increment in the ratio about every five years, particularly noticeable from 1841 to 1857.

[1] *Edinburgh Medical and Surgical Journal*, vol. xxxvii, January, 1832.

From 1857 to 1876, although the average ratio is not so high, yet every two or three years there is a marked increase. From 1877 to 1895 the ratios are not particularly high, but the variation from a low rate to that of a comparatively high one is noticeable. Since 1895 the ratios are lower than in previous years, but there is still a certain amount of variation. For the years from 1902 to 1904, inclusive, there has been a diminution each year.

FIG. 30.



Ratio of mortality of scarlet fever per 10,000 of the population in Boston, for sixty-five years, 1840 to 1904, inclusive.

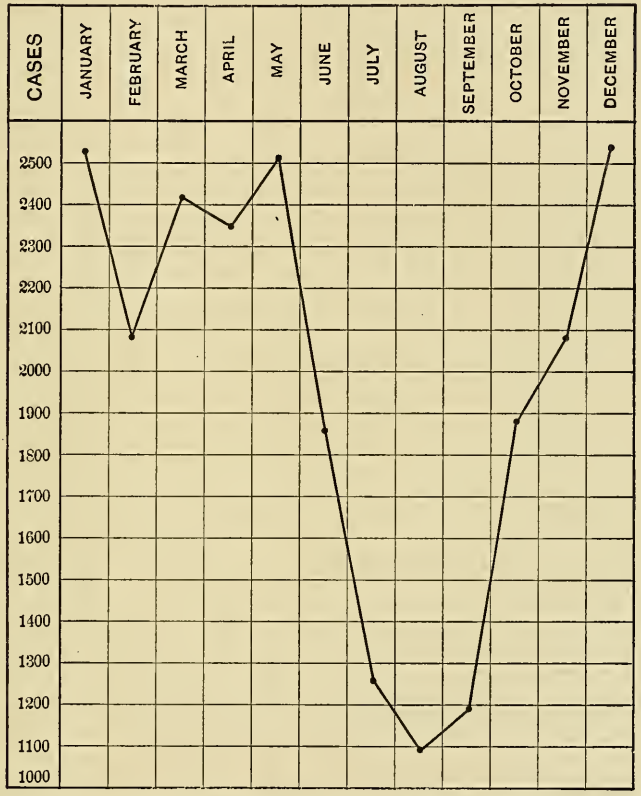
Etiology.—As scarlet fever is an infectious disease, the influence of climate on its prevalence cannot be very great, except indirectly. The habits of life in warm climates are so essentially different from those in temperate climes that scarlet fever is not so likely to gain a foothold in the former as in the latter. The aggregation of individuals is always an important factor and cities always suffer more than rural districts. The tenement house increases the prevalence of the disease. In the United States, in cities where one family among the middle and lower classes occupies a small house, the disease is not nearly so common, as a rule, as in the cities where three or more families live in tenement houses.

Where large numbers of children are brought into immediate contact, as in schools, scarlet fever is sure to prevail to a greater or less extent from the fact that there are always in any thickly-settled community a certain number of individuals suffering from mild and unrecognized attacks. Fig. 31 shows the number of cases of scarlet fever in Boston by months, reported to the Board of Health for fifteen years, 1890 to 1904, inclusive, comprising 23,835 cases.

During July and August, when the schools are not in session, the number of cases is very much less than during November, December, and January; the increase commences in September and there is a very marked increase from September to October, from October to November, from November to December; December and January are practically the same. There is a diminution from January to February, but no perceptible diminution in March, April, and May as compared with February. The number reported for the months of June in these fifteen years was 1,863, while the number

reported for the months of October for the corresponding years was 1,883, practically the same, so that meteorological conditions can have no particular influence, except indirectly. The better that school-rooms and houses are ventilated, the less the possibility of infection. The majority of these cases of scarlet fever occurred in children of the school age. The importance of a medical inspection of schools, in order that children with mild attacks of the disease should be excluded, is evident.

FIG. 31.



Cases of scarlet fever in Boston, by months, reported to the Board of Health from 1890 to 1904.

Susceptibility.—The majority of individuals are susceptible to scarlet fever to a greater or less extent, but this susceptibility is in an inverse ratio to the age. After fifteen years there seems to be an acquired immunity which may be explained to a certain extent by previous unrecognized mild attacks.

Contrary to the generally received idea, nursing infants are particularly susceptible. The only reason why more infants do not contract scarlet fever is the fact that they are not exposed to such an extent as older children. If a case of scarlet fever appears in a family where there is a nursing infant, it is much more likely to contract the disease than the other children of the

family. The following table gives the age incidence in 5,000 cases of scarlet fever:

Under 1 year	42	9 to 10 years	250
1 to 2 years	182	10 to 11 years	202
2 to 3 years	381	11 to 12 years	143
3 to 4 years	569	12 to 13 years	120
4 to 5 years	551	13 to 14 years	81
5 to 6 years	557	14 to 15 years	48
6 to 7 years	522	15 to 18 years	125
7 to 8 years	424	18 to 23 years	245
8 to 9 years	323	Over 24	235
		Total	5000

It will be seen that from three to six years the incidence was extremely high, and that after six years there is a marked diminution. Although the rate under one year of age is quite low it does not prove that infants are not susceptible to the disease, but it does prove that a certain number, if exposed, do contract it. These statistics are based on hospital cases.

A vast amount of laboratory work has been done in investigating the cause of scarlet fever. Some observers have claimed that the disease is due to a streptococcus morphologically similar to the streptococcus pyogenes. In no instance, however, in these investigations has Koch's law been carried to its full extent. As the lower animals are not susceptible to scarlet fever the chain of argument used by those who claim that a streptococcus is the cause of the disease has this weak link. It is perfectly true that, in the majority of instances, streptococci are found in cultures from the throat of scarlet fever patients, but the presence of this organism is a complication, and although it may be a very important factor in increasing the severity of the attack and contributing to a fatal issue, it has not been satisfactorily demonstrated, thus far, that it is the cause of the disease. Baginsky, D'Espine, and Moser believe that scarlet fever is due to a streptococcus. Heubner, Marmorek, Slawyk, Pearce, and other observers, claim that the origin of the disease is due to some agent which has not been, as yet, discovered. The theory has been advanced that scarlet fever is produced by a symbiosis of a streptococcus and an unknown virus. Streptococci are very frequently found in the urine of scarlet fever patients but this does not prove that this organism is the cause of the disease.

In 1899, Page in cultures from the throats of twenty-four patients ill with scarlet fever found streptococci in twenty-three instances. In 1903, Weaver made a series of cultural investigations from the throats of scarlet fever patients. His conclusions are as follows:

1. "Streptococci are almost always, if not constantly, present in the throat in cases of scarlatina. In the early stages they are usually in very large numbers, becoming less numerous as the disease progresses.

2. "The streptococci in the throat of scarlatina patients resist drying as long as the other bacteria usually present, and they often outlive all other forms, being alive as long as ninety days after the material is collected.

3 "These streptococci remain alive for a long time in milk.

4. "A small amount of sugar in nutrient media increases their value for the cultivation of streptococci.

5. "Streptococci from scarlatinal anginas are not different from streptococci from other sources so far as cultural and morphologic peculiarities are concerned."

Hektoen in 1903 examined the blood during life in scarlet fever with special reference to streptococcæmia. He says: "The conclusions that suggest themselves from this work so far as scarlatinal streptococcæmia is concerned are that streptococci occasionally may be found in the blood of cases of scarlet fever that run a short, mild, and uncomplicated clinical course; that streptococci occur with relatively greater frequency in the more severe and protracted cases of scarlet fever in which there also may develop local complications and clinical signs of general infection, such as joint inflammations, but even in the grave cases of this kind spontaneous recovery may take place; and finally, that streptococcæmia may not be demonstrable in fatal cases of scarlet fever. The theory that scarlet fever is a streptococcus disease does not seem to receive any direct support from this work."

The *Streptococcus scarlatinæ* of Klein and Gordon or the *Streptococcus conglomeratus* of Kurth is polymorphic and shows a tendency to oval and rod-shaped elements. It is a nonliquefying organism. The chain formation in bouillon is more marked than in the *Streptococcus pyogenes*, which grows more rapidly. The colonies on agar are smaller, more opaque, and more irregular than those of other streptococci. In milk this organism causes rapid coagulation. Newman gives the following chief diagnostic features of this organism: (1) "The sediment growth in broth cultures; (2) the rapid coagulation of milk; (3) the acid reaction in litmus milk; (4) the character of the agar colonies."

In 1904, Grünbaum[1] attempted to infect lower animals with scarlet fever. In describing his experiment he says: "Various modes of infection were tried; by clothes, skin peelings, swabs from the throat of a patient, culture of *Streptococcus conglomeratus*, and the heart blood removed shortly after death with a syringe. With the last only rhesus monkeys and rabbits were infected. The streptococcus isolated proved very fatal to the latter; in the monkey it merely caused suppuration. Some of the material was from a very malignant case described by de Boinville. In the chimpanzee the only positive result was obtained when the throat was rubbed with the swab from a patient's throat. A scarlatinal tonsillitis ensued, but no rash or extensive desquamation." Although the *Streptococcus conglomeratus* was isolated from the throat of one of the animals, as there was no eruption and no extensive desquamation, it is reasonable to suppose that the chimpanzee did not have scarlet fever.

There has yet been no discovery that proves definitely that scarlet fever is a bacterial disease and the work of Mallory would seem to demonstrate that the cause of the disease is probably a protozoön.

Pathology.[2]—The gross pathological lesions of scarlet fever are slight.

[1] *British Medical Journal*, April 9, 1904.

[2] The section on Pathology was written by F. B. Mallory, M. D., Associate Professor of Pathology, Medical Department, Harvard University; First Assistant Visiting Pathologist, Boston City Hospital.

This account of the pathology of scarlet fever is based in part on the paper by Dr. R. M. Pearce, ("Scarlet Fever, its Bacteriology, and Gross and Minute Anatomy," *Medical and Surgical Reports of the Boston City Hospital*, 1899, vol. x, pp. 39–82), and in part on the study of the same cases which he used and of other cases which have come to autopsy at the Boston City Hospital since his paper was published.

The diffuse exanthem of the skin and the rash often present in the mucous membrane covering the tonsils, palate, and cheeks usually do not show after death. A false membrane on the tonsils may occasionally be seen. Desquamation is often evident if death occurs in the later stages. The only constant gross change found postmortem is a hyperplasia of the lymphoid tissue in every part of the body. On the other hand important lesions may occur in certain organs as sequelæ or complications. Although the cause is still unsettled, the evidence so far obtained points to the skin and to the mucous membrane of the mouth and pharynx as the site of the infectious agent. The changes produced in them may be regarded as the primary lesion of the disease and those produced elsewhere as sequelæ and complications.

The lesions of the skin are interesting histologically. The bloodvessels of the corium show marked dilatation, more especially near the epidermis and in the papillæ. The superficial lymphatics and lymph spaces likewise show dilatation in the same situation, that is, just beneath the epidermis and in the papillæ. The exudative phenomena which take place in the skin vary with the intensity of the disease. They may be slight or very prominent. In a well-marked case the leukocytes are abundant in the dilated bloodvessels of the corium and many have emigrated from the bloodvessels and can be found in the corium and invading the epidermis. They consist chiefly of polynuclear and non-granular leukocytes, but lymphoid cells and rare eosinophiles are found among them. The leukocytes are collected around the blood- and lymph vessels and also in the tops of the papillæ. The lymphatics contain serum and an occasional leukocyte. In the epidermis the leukocytes are usually elongated and distorted, owing to fixation while in amœboid motion between the epithelial cells, but some show a greater or less degree of necrosis as indicated by the deeper staining of their protoplasm with acid dyes and the characteristic changes in the nucleus. Similar changes occur in the epithelium of the hair follicles and of the ducts of the coil glands near the epidermis, never deep in the corium.

The epidermis shows but slight changes beyond swelling of the cells in the stratum lucidum in consequence of œdema: the limits of the cells are well defined, but the protoplasm is reticulated and the nucleus often lies in a vacuole. Occasionally elsewhere in the epidermis a necrotic epithelial cell is found. In contrast to these degenerative changes many mitotic figures are present in the rete Malpighii.

The inflammatory exudation continues for several days and is, perhaps, most abundant in those cases which die on the fifth to the tenth day from the onset of the eruption. By the twelfth to the sixteenth day the leukocytic infiltration has nearly disappeared.

In the *tongue* the pathological changes are similar to those in the skin, but they begin earlier and are more marked. There is the same dilatation of the bloodvessels and lymphatics in the corium and an abundant infiltration both of the corium and of the epithelium with polynuclear leukocytes. The infiltration is always greatest in and over the papillæ, and affects the papillæ more at the tip than at the base of the tongue. The marked involvement of the papillæ explains their enlargement during life.

The mucous membrane of the *pharynx*, *soft palate*, and *tonsils*, show changes similar to those in the tongue.

These degenerative and exudative phenomena in the skin and mucous membranes probably represent the primary essential lesion of scarlet fever.

EXPLANATION OF FIGURES IN PLATE XV.

The drawings were made with the Abbe camera lucida; projection on to table. Zeiss apochromatic homogeneous immersion 2.0 mm., apert. 130, compensation ocular 6.

Figs. 1 and 2 show numerous large and small scarlet-fever bodies (stained light blue) in and between the epithelial cells of the rete mucosum. In Fig. 1 is a large body in a lymph space of the corium just underneath the epidermis. Several of the bodies suggest fixation while in amœboid motion.

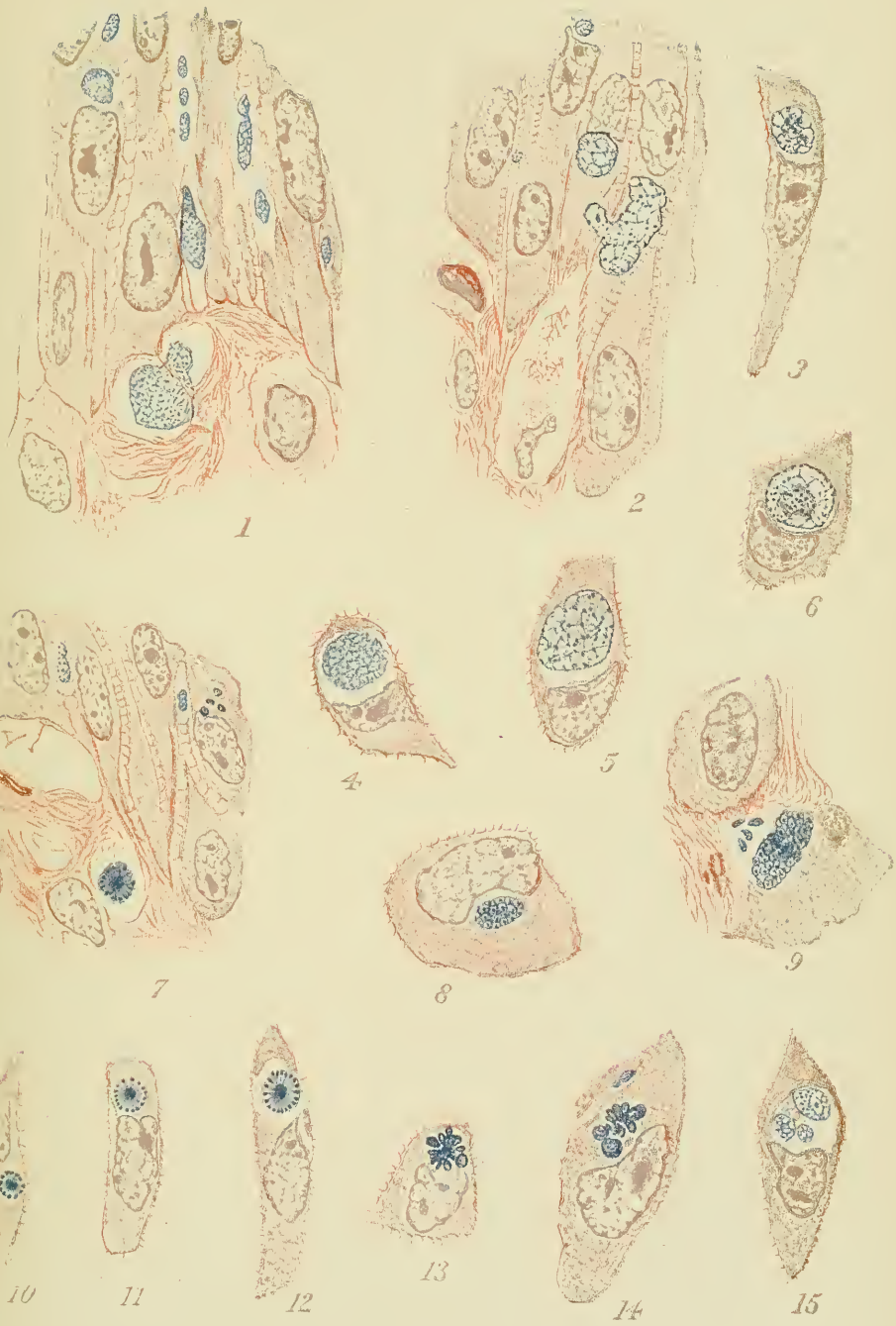
Figs. 3, 5, and 6 are coarsely reticulated forms which may be degenerate forms of the scarlet-fever bodies, or stages in sporogony.

Figs. 4, 8, and 9 probably represent stages preceding the radiate bodies. In Fig. 9 the bodies lie in a lymph space. It shows also four small forms which have just got free from a rosette.

Figs. 7, 10, 11, 12, 13, 14, and 15 show different stages in the development of the radiate bodies.

Fig. 10 is the earliest stage: there is a distinct central body and a definite, regular arrangement of granules at the periphery. Figs. 7, 11, and 12 show a little later stage of development; 11 and 12 are optical sections, while 7 is a surface view. Moreover, in Fig. 7 the body lies free in a lymph space in the corium. The segments begin to show a certain amount of lateral separation from each other. Fig. 13 is a still later stage: the segments are increasing in size and are more or less free from each other, although most of them are still attached to the central body. In Fig. 14 the segments are all free and enlarging, although still grouped around the central body. In Fig. 15 the bodies are still grouped around the central body, which is free and stains deeply with eosin. (Mallory.)

PLATE IV



The causal agent of the lesion has not yet been definitely determined. It seems fairly probable, however, that it is not a bacterium, certainly not the *Streptococcus pyogenes* which is so often found in the blood as a secondary invader. The recent discovery,[1] therefore, in the skin of scarlet fever cases, of certain bodies which resemble protozoa is interesting and possibly of much etiological significance.

The bodies in question usually vary from 2 to 7 μ in diameter, but occasionally measure 10 to 12 μ. They may be divided into two sorts, the granular and the radiate. The granular bodies are usually finely but occasionally coarsely meshed and show all variations in size between the limits given. They often contain one or more small but distinct vacuoles. They vary in shape from round to elongated and lobulated forms suggesting amœboid motion. The radiate bodies vary in diameter from 4 to 6 μ and are almost invariably spherical in shape. They contain a central round body, around which are grouped on optical section 10 to 18 narrow segments which in some cases are united, but in others are sharply separated laterally from each other. Occasionally some of the segments are larger than the others, and in their staining reaction and form closely resemble the smallest granular bodies. Sometimes all the segments are seen as small free bodies which still surround the central body, or seem as if they had been fixed while moving away from it between the cells. (Plate XV.)

These two kinds of bodies are found in three situations: lying in vacuoles in the epithelial cells of the epidermis, to a less extent between these cells, and free in the lymph vessels and spaces of the corium just beneath the epidermis. When within epithelial cells they usually cause indentation of the nucleus. The bodies are not distributed evenly, but usually occur in small clumps. Moreover, the skin from one location may show them chiefly in the lymph spaces of the corium, especially in the papillæ, while in that from another situation they may be almost entirely between or in epithelial cells. They are always least numerous where leukocytes are most abundant.

At the time of the first description of these bodies they had been found in skin taken probably from over the chest or abdomen. Since then Duval has found them in five other more recent cases which have come to autopsy. The bodies were present in skin from the chest, abdomen, groin, and inner aspect of the arm. Led by their presence in the lymph vessels and between the epithelial cells of the epidermis to the belief that the bodies might be drawn out with the serum, he devised a simple method[2] of producing rapid vesication and was able to obtain the bodies often in large numbers from vesicles produced in the groin in five out of eighteen cases. The serum was practically free from cells and the bodies could be stained in coverslip preparations by the same methods used for blood preparations.

It is doubtful if these bodies are degenerations, because they occur not only within cells but free between them and within lymph spaces of the corium. It seems much more probable that they are protozoa and have an etiological relation to scarlet fever.

In addition to these primary lesions of the skin and of the membranes of the mouth and pharynx, certain lesions due to secondary infections with the

[1]Mallory, F. B., "Scarlet Fever; Protozoön-like Bodies Found in Four Cases," *Journal of Medical Research*, 1904, vol. v, 483–492.

[2]Duval, C. W., "Die Protozoen des Scharlachfiebers." *Virchow's Archiv.*, 1905, vol. clxxix, 485–498.

Streptococcus pyogenes, less often with staphylococci or pneumococci, are relatively common and complicate the pathological changes due to the causal agent of scarlet fever These secondary processes are, in the order of their frequency: acute bronchopneumonia, acute inflammation of the middle ear with or without extension to the mastoid cells, suppuration of cervical lymph nodes, acute pleuritis, and inflammation of the antrum of Highmore. The less frequent complications are abscess of the lung, ulceration and abscess formation in the upper respiratory tract, acute endocarditis, inflammation of the sphenoidal sinus, and metastatic abscesses of the kidney. Some of these lesions deserve mention.

The bronchopneumonia may occur as small discrete or as large confluent nodules. Areas of atelectasis are often associated. The bronchopneumonia is most often due to streptococci, but staphylococci or pneumococci are sometimes the cause. Microscopically the exudation in the lung does not differ from that found in bronchopneumonia in other infectious diseases, except, perhaps, in the number of plasma cells present. They usually occur in small numbers among the other elements of the exudation, but are found in greater abundance in the walls of the alveoli. They are also often present in the bloodvessels. In all these situations their nuclei often show mitosis.

Acute inflammation of the *middle ear* occurs in many cases and is usually bilateral. Rarely the process extends to the mastoid cells. In the majority the exudation is purulent, but in others it is mucoid with an abundant mixture of pus cells. As a rule the infection is due to streptococci and may occur as early as the third day. Less often a similar infection of the *antrum of Highmore* and still more rarely of the *sphenoidal sinus* may take place, with the production of a purulent or mucoid exudation.

A general infection or *septicæmia*, usually with the streptococcus pyogenes, is of common occurrence in fatal cases and must have great clinical significance. As a result of these secondary infections it is difficult to determine in all cases just what part of the systemic lesions present in the different internal organs is due to toxic substances derived from the infectious agent of scarlet fever and what part is due to the toxic substances derived from the bacteria present as secondary invaders. Still a certain number die from uncomplicated scarlet fever, and from these a true picture of the systemic lesions caused by the scarlet fever organism can be obtained. Like the general systemic lesions in diphtheria they are characteristic but not specific.

The muscle fibers of the *heart* in a certain proportion of cases show degenerative changes, of which the most important is that which is associated with the deposit of fat in fine droplets in the fibers.

Ordinarily the *spleen* is not enlarged. It is firm, and the capsule is smooth but not tense. There is no increase of pulp, but the Malpighian bodies usually are decidedly enlarged and stand out prominently as gray to white areas on a dark reddish background. In some cases, however, the spleen is enlarged and soft, the pulp greatly increased, and the Malpighian bodies indistinct. The cause of these differences is not apparent. It does not seem to depend on the age of the patient, the stage of the disease, or the presence or absence of general infection.

Microscopically, in stained preparations the centres of the enlarged Malpighian bodies appear pale, while the periphery is stained deeply. The pale centres are composed chiefly of large phagocytic cells derived by proliferation from the endothelial cells lining the reticulum of the lymph nodu-

les. The lymphoid cells in the centres of the nodules have for the most part been incorporated and digested by the phagocytic cells in whose protoplasm only fragments of them can be found. The phagocytic cells are usually more or less fused together so that their outlines are made out with difficulty. In some cases they undergo necrosis and are transformed into a hyalin material which stains deeply with eosin. The deep staining of the periphery of the Malpighian bodies and, aside from the phagocytic cells, the chief cause of their enlargement are due to the presence of great numbers of plasma cells many of which show mitosis. The infiltration with plasma cells likewise occurs abundantly everywhere in the pulp, both around the bloodvessels and along the trabeculæ. They are also present within the bloodvessels.

The veins of the spleen often present a curious condition. Collections of cells take place beneath the lining endothelium and in some cases cause irregular projections into the lumina so as almost to occlude them. The cells which collect in this manner are principally lymphoid and plasma cells.

The changes in the *gastro-intestinal tract* are slight and mostly due to secondary infections. Ulceration of the œsophagus and small abscesses in the mucous membrane have been noted. Hemorrhages may occasionally be found beneath the mucous membrane of the stomach and intestine. The one constant lesion is a more or less well-marked hyperplasia of the lymph nodules of the intestine. In severe attacks with death early in the disease, the Peyer's patches are exceedingly prominent, and the swelling may be almost as marked as in typhoid fever. The solitary lymph nodules of the large intestine may be equally prominent.

Microscopic examination of the *stomach* often shows more or less necrosis of the lining epithelium and numerous leukocytes both on the surface of the mucous membrane and in the lumina of the glands. The centres of the lymph nodules are occupied by numerous large phagocytic cells in which are often fragments of the ingested lymph cells.

The changes in the lymph nodules of the *intestine* are very similar to those in the stomach. There is a marked proliferation of endothelial cells in the centres of each and a corresponding disappearance of the lymphoid elements which have been incorporated and digested. In the *appendix* the lymph nodules show a marked degree of the same process.

The changes in the *liver* are usually slight and chiefly of a degenerative character,—fatty degeneration being the most important. Necroses occur rarely; two types have been observed, the central and the focal. In a marked case of the latter, there occurred everywhere on the surface and throughout the substance of the liver small yellowish, opaque, non-purulent, non-elevated areas, each about 1 mm. or less in diameter. They probably represent miliary infarctions.

In the *kidneys* acute degenerative changes are common, especially cloudy swelling and fatty degenerations. The most interesting and important lesion is acute interstitial non-suppurative nephritis, which is fairly common. The process varies from slight to very extensive changes. In marked cases the kidneys are enlarged and the capsule peels readily, leaving a smooth pale watery surface. On section the cortex is swollen and the cut surface is mottled with small grayish, translucent areas, most numerous in the intermediate zone and in the adjoining cortex. These areas are irregular, round

or linear in shape. They are present in a less degree in the cortex immediately beneath the capsule. Small hemorrhages may occur here and there. Minor degrees of the process can be recognized only by the microscope.

Histologically the process consists of a cellular infiltration, most marked in the cortex just beneath the capsule, around the glomeruli, and around the bloodvessels in the intermediate zone. The cellular areas are composed chiefly of plasma cells, but a certain number of lymphoid cells and polynuclear leukocytes are usually associated with them. Mitotic figures are often present in the plasma cells. Many plasma cells are also found in the straight vessels of the pyramids. It is evident that they migrate from these vessels into the adjoining tissue. The degenerative changes in the renal epithelium are no more marked in these cases of acute interstitial nephritis than in those in which no interstitial changes are present. Although acute capsular glomerulonephritis is generally believed to occur not infrequently after scarlet fever, no case of it has yet been observed in the rather large series of autopsies which have been made on scarlet fever patients at the Boston City Hospital.

The *lymph nodes* in all situations are enlarged, firm, and on section pale and watery. They are never soft and pulpy unless secondarily infected. The cervical lymph nodes show the greatest enlargement, the axillary and the inguinal the least. The changes in them are not constant in all cases, but in general they are similar to those in the lymph nodules of the spleen. The bloodvessels are congested. The lymph sinuses are dilated and contain many large endothelial cells which are frequently phagocytic. The inclusions are generally lymphoid cells and red blood corpuscles, and may be very numerous, ten to twenty in a cell. The sinuses also contain numerous plasma cells.

The lymph nodules are much enlarged and contain in their centres numerous large, lightly staining, endothelial cells, which are so closely packed together that their outlines are usually made out with difficulty. They are often phagocytic and contain fragments of lymphoid cells.

The chief change in the *bone marrow*, aside from numerous eosinophiles, is the presence of great numbers of cells which cannot be distinguished from plasma cells. They frequently show mitotic figures and correspond in every way with the cells found in the bloodvessels everywhere and in the intestitial tissues of the kidneys.

The other organs of the body are negative, except that the *thymus gland* in some cases contains many phagocytic cells in which are incorporated lymphoid cells and red blood corpuscles.

Incubation.—There is a marked difference in opinion regarding the incubation stage, some giving as short as twenty-four hours, others as long as twenty-one days. Much of this discrepancy is due to faulty observation, and also to the fact that, although there may be a certain definite known exposure to the disease, there is also just as likely to be an unknown exposure to a mild and unrecognized attack of scarlet fever. Too much stress has been laid upon an absolute definite time of incubation in the acute infectious diseases. The question naturally arises as to why scarlet fever should have a much shorter period of incubation than the others. In the few instances where individuals have been inoculated with the blood of scarlet fever patients, it has been found that three or four days elapsed before the onset of symptoms. This would seem to be a sufficient answer to the statement that the period of

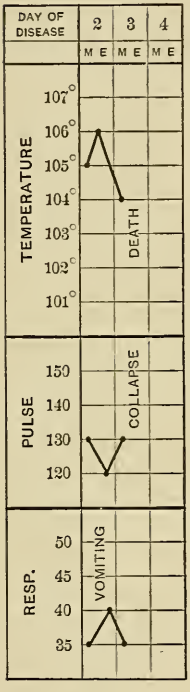
incubation of scarlet fever may be twenty-four to forty-eight hours. When smallpox is inoculated the period of incubation is considerably shorter than when the disease is contracted in the natural way, and it is reasonable to suppose that similar conditions prevail in scarlet fever. When a patient in a general hospital has an attack of scarlet fever and is removed as soon as the diagnosis is made, other patients in the same ward, if susceptible, do not show any symptoms of scarlet fever for at least a week or ten days, and, in some instances, twenty days. At the South Department, of the seventy-four nurses who contracted scarlet fever when on duty, in only one instance was the period of incubation as short as six days. It may be said that a person exposed to scarlet fever does not always contract the disease at once, but if the period of incubation is so short as twenty-four or forty-eight hours, certainly some of these individuals would have contracted the disease in that time. Quite a number of instances have come to the knowledge of the writer where it was definitely known that there was only one exposure to scarlet fever and where the disease became manifest twenty days after this. It is a very frequent occurrence for a child of the school age to be admitted to the South Department ill with scarlet fever and the other children in the same family too young to attend school do not show any symptoms of the disease for a week or ten days. This has been of such frequent occurrence that it suggests that the period of incubation cannot be as short as twenty-four hours. In 1861, Trousseau said that neither in measles nor in scarlet fever could the duration of the latent period be rigorously determined. Some few years later Obermeier said that the incubation period of scarlet fever was unknown.

Hagenbach-Burkhardt reports 57 cases in which he gives the incubation period of 35 cases as over seven days, under eight days 4 cases, nine days 2 cases, ten days 1 case, eleven days 5 cases, twelve days 1 case, thirteen days 4 cases, fourteen days 2 cases, fifteen days 5 cases, seventeen days 2 cases, eighteen days 1 case, nineteen days 2 cases, and over twenty days 6 cases. Veit says that the period of incubation may be twelve to fourteen days. Paasch reports a case in which it was twelve days. Gerhardt and Reinhold give eleven to thirteen days. Bawy reports a case in which the period of incubation was twenty-one days; Trojanowsky one in which it was twenty-eight days. Where there is a difference of opinion regarding the period of incubation it is evident that these different observers cannot be all correct or all incorrect. The most logical conclusion is that the mean time of these different observers, twelve to fourteen days approximately, is probably the true period of the incubation of scarlet fever. From the study of over 5,000 cases of scarlet fever in many of which the time of exposure was definitely known, notwithstanding the statements of the authorities already given, the writer is thoroughly convinced that the period of incubation is variable; that the limits are practically from four to twenty days, with an average of ten to fourteen days. This conclusion has been reached not from literature, but from personal observation and clinical study.

Symptoms.—Five distinct varieties of the disease are recognized. First, the fulminating, in which the patient succumbs in from twenty-four to forty-eight hours. This is frequently mistaken for hemorrhagic smallpox and, on the other hand, hemorrhagic smallpox is mistaken for it. Persistent vomiting is a prominent symptom. The angina is not particularly marked. Diarrhœa frequently occurs. If the patient dies within twenty-four hours

the characteristic eruption does not appear, and the diagnosis must be based on the constitutional symptoms. If the patient lives forty-eight hours there is a very general erythematous blush, but the eruption does not assume the characteristic appearance because the patient does not live long enough.

Fig. 32.

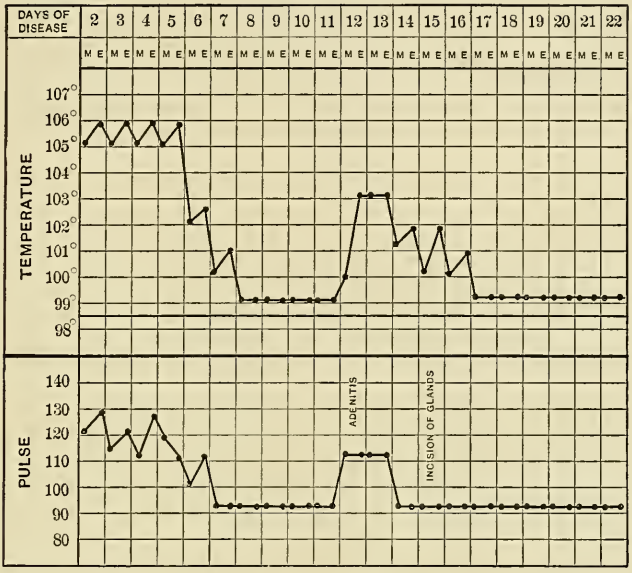


The erythema is an extremely brilliant red and in some instances the skin is almost a mahogany color. Delirium of a violent type is a prominent symptom. The temperature is extremely high, from 105° to 106° F. (Fig. 32). Second, a malignant form, in which the temperature is extremely high from the outset, frequently reaching 105° F. (Fig. 33). The eruption is extremely brilliant, and it is impossible to make out the punctate appearance except in small areas scattered here and there. Delirium of an active type, and in some instances of the low muttering variety, is usually present. There is marked dysphagia and sometimes so much swelling of the fauces as to interfere with respiration. The tongue is heavily coated. Third, a moderately severe variety, in which the temperature reaches 104° (Fig. 34) There is a profuse nasal discharge and marked anginose symptoms. Streptococcæmia is always present in this form. The patient, as a rule, is not actively delirious but in a state of semi-stupor. The eruption is not extremely brilliant, but has the characteristic punctate appearance. Fourth, a form characterized by a certain amount of angina, a not particularly high temperature (Fig. 35), a somewhat faint but characteristic punctate eruption on the body and in the roof of the mouth. The eruption is accentuated in the axillæ and in the groins. Fifth, a variety in which the anginose symptoms are particularly marked, and the cutaneous manifestations in abeyance. This variety has been termed *scarlatina sine eruptione* (Fig. 36). There is no sharp and dividing line between these different varieties but to understand the disease it is necessary to make this arbitrary division. Scarlet fever varies more in intensity than any of the other exanthemata, and this is the reason why the disease is so prevalent, as many cases are not recognized and therefore not isolated.

The onset of scarlet fever, as a rule (to which, however, there are many exceptions), is abrupt. The attack may commence with a slight headache, a feeling of chilliness not amounting to a rigor, a slight sore throat, nausea and vomiting. In children the attack frequently begins with a convulsion. In some instances there may be a feeling of malaise for three or four days before the onset of the characteristic symptoms. Of 5,000 cases observed at the South Department of the Boston City Hospital, nausea and vomiting as an initial symptom occurred in about 80 per cent. In 10 per cent. of the remaining cases the patients were too ill to give any history. Some observers have given the percentage of initial vomiting a little lower. It is reasonable to conclude that in about three-fourths nausea and vomiting are the initial symptoms. The characteristic eruption which commences, as a rule, on the chest may appear two or three hours after the vomiting or may be deferred

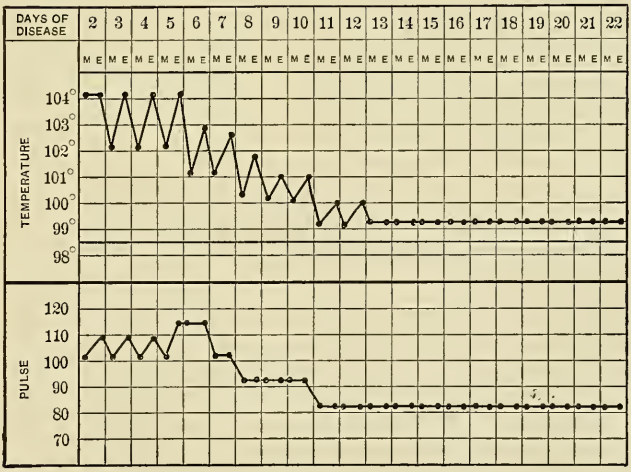
for twelve to fourteen hours. In rare instances the eruption does not appear for twenty-four hours. Angina of greater or less severity is present, as a

Fig. 33.



rule, in every attack. It may be so slight as to escape detection or so severe as to be mistaken for diphtheria. An exudate which has a certain similarity to that of diphtheria frequently appears on the tonsils and often gives rise to error. The uvula is intensely congested and is frequently œdematous.

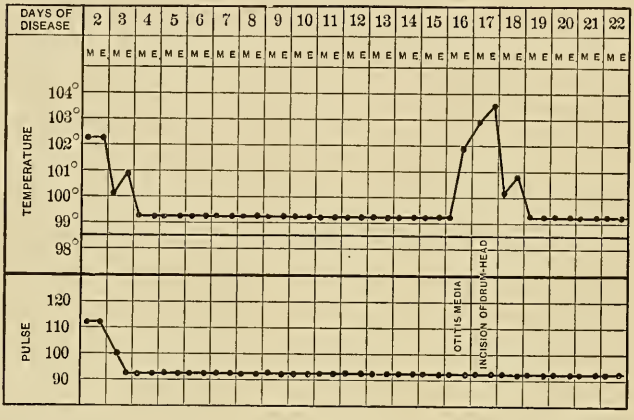
Fig. 34.



A punctate eruption is frequently observed in the roof of the mouth. The tongue is frequently coated with a creamy white fur through which the

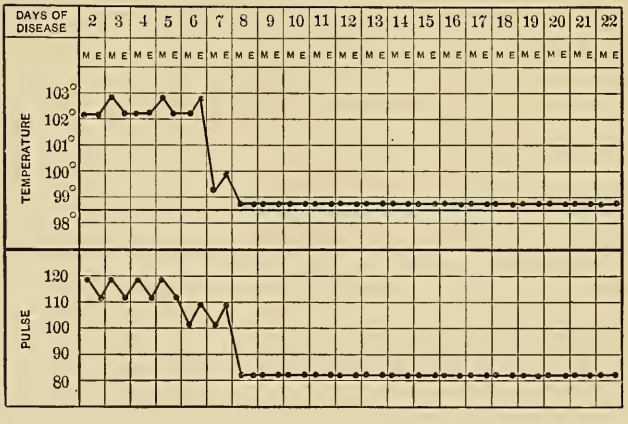
papillæ can be seen giving the appearance known as the strawberry tongue. The enlargement of the papillæ of the tongue at the tip and edges is a constant symptom and if a careful examination is made will be found in every case, although in some instances it is so slight that it escapes detection. After

FIG. 35


DAYS OF DISEASE
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
104°
103°
102°
101°
100°
99°
98°
PULSE
120
110
100
90
OTITIS MEDIA
INCISION OF DRUM-HEAD

the tongue is clean the papillæ become more prominent and look like minute buttons studding the surface. In the interspaces the mucous membrane is reddened and has a peculiar glazed, wrinkled appearance. In some instances the tongue looks as if it had been varnished, it is so smooth and dry. The papillæ sometimes have an appearance very much as if small grains of cayenne pepper had been sprinkled on the surface of the tongue. The circumvallate papillæ, as they are always more or less prominent, do not seem to be specially increased in size in scarlet fever, but it is the papillæ at

FIG. 36.

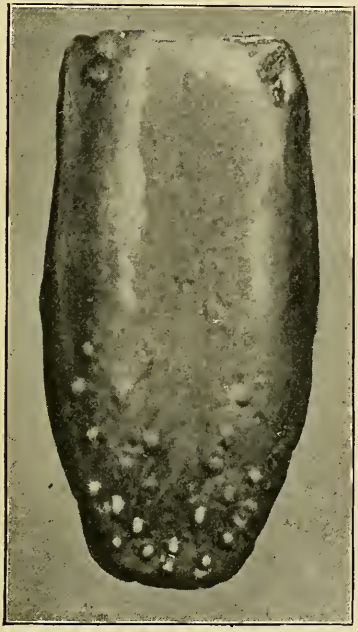

DAYS OF DISEASE
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
103°
102°
101°
100°
99°
98°
PULSE
120
110
100
90
80

the tip and edges of the tongue that present the appearance just described. The importance of the appearance of the tongue in diagnosis is very great, and frequently after the disappearance of the eruption and before desquamation takes place is the only symptom on which reliance can be placed. The

figures (37 and 38) are diagramatic, and therefore the enlargement of the papillæ is exaggerated.

The history of a typical attack of scarlet fever of an extremely mild form is as follows: The child has a sudden attack of vomiting, complains of slight headache but after vomiting seems to feel better. Five or six hours later the body is covered with a slight erythematous blush, with a faint punctate appearance. This fades in twelve hours, sometimes in six, and the child is apparently well. There is no isolation, and five or six days later other members of the family have attacks of scarlet fever of more or less severity. If the child goes to school he infects some of his schoolmates. Some few years ago a child in an institution where there were 150 children had an attack of

Fig. 37.



Papillæ of the tongue about the third day.

Fig. 38.

Papillæ of the tongue on the ninth day.

scarlet fever similar to the one just described, and infected 25 of the inmates. No physician was called, as the child apparently was not ill; the rash was so evanescent that it escaped the observation of the matron. The writer has seen some 8 instances of outbreaks traced to similar mild attacks.

As scarlet fever varies in intensity, so does the temperature. As a rule, the more brilliant the eruption the higher the temperature. In a study of 3,000 cases with regard to the temperature it was found that 102 had a temperature of 99° F.,411 had a temperature of 100°, 470 a temperature of 101°. In 589 the temperature reached 102°; it was 103° in 575 cases; it was 104° in 484 cases; in 330 cases it was 105°; and in 39 instances was 106°. In 2,487 cases, the temperature remained above 100° one day in 414, two days in 558, three days in 498, four days in 315, five days in 204, six days in 153, seven days in 102, eight days in 114, nine days in 45 and ten days in 84 cases. The temperature in some cases falls by crisis and in others by lysis.

Eruption.—This is a punctate erythema and varies in a marked degree according to the type of the disease; sometimes the entire surface of the body is of a brilliant scarlet hue and it is impossible to make out the individual puncta. In other cases in certain portions of the body there will be simply a blush, and in other portions distinct puncta can be distinguished. In moderately severe attacks there is a marked redness of the palms and soles which have a hard and dry feeling. Numbness of the hands is not infrequent. As a rule, the eruption is accentuated on the axillæ, groins, and popliteal spaces. The papillæ of the skin are enlarged in moderately severe attacks. Miliary vesicles frequently appear, although this is not a part of the disease but due to the high temperature. The skin has a peculiar harsh and dry feel, which is particularly marked after the fading of the eruption, or, in other words, the skin of the patient, if a child, resembles that of an old person. It has a papery feel and wrinkles when the hand is passed across the abdomen. In the colored race there is a peculiar appearance of the skin which it is impossible to describe, the hue being of a more intense black and without the lustre seen in health.

The eruption generally commences on the trunk and extends upward to the neck and downward to the extremities. As a rule, there is no eruption on the face. The cheeks may be extremely red, but the upper and lower lips are pale, giving the appearance known as mouth pallor, which is a very constant symptom in moderately severe attacks. Frequently there is an intense burning heat of the skin, sensible to the touch, although the temperature may not be particularly high. As the character of the disease varies greatly, so the eruption differs in a like degree from a transient erythema lasting from twelve to twenty-four hours to an extremely brilliant efflorescence lasting three or four days.

Plate XVI gives a very good idea of the eruption of scarlet fever of a not very severe type. The herpetic eruption near the commissures of the lips is very well shown. This is a very frequent condition in scarlet fever. The mouth pallor can also be seen.

Delayed rashes sometimes occur; that is to say, a patient will have the angina of scarlet fever, and six, seven, and in some instances ten, days may elapse before the eruption appears. During this time the patient has a high temperature with marked throat symptoms and an exudate on the tonsils, cultures from which show the presence of streptococci.

Cervical adenitis is a very common symptom, and may appear early in the course or be delayed until convalescence. In an analysis of 5,000 cases of scarlet fever the cervical glands were enlarged in about 50 per cent. Suppuration took place in about 8 per cent.

The kidneys in scarlet fever as a rule are affected to a greater or less extent. Albuminuria is present in a large proportion. In a series of 1,000 patients it was found that in about 28 per cent. no albumen was found; the slightest possible trace was found in 40 per cent.; a very slight trace in 4.5 per cent.; a slight trace in 10 per cent.; a trace in 7 per cent.; and a large trace in 3 per cent. If the amount of albumen was sufficiently large to be estimated by fractions of 1 per cent. it was observed that about 3 per cent. had one-tenth of 1 per cent.; 4 per cent. had one-eighth; and 2 per cent. had one-fourth. There were 15 instances in this series in which the amount of albumen was one-half of 1 per cent. Six of these patients died. A small amount of albumen, especially if a large quantity of urine is passed, does not

PLATE XVI

Scarlet Fever. Stage of Eruption.

necessarily indicate that the patient may not have a uræmic convulsion. A patient may seem to be progressing favorably, passing a sufficient amount of urine with only a trace of albumen, when suddenly he has a convulsion and dies in a short time. In 5,000 cases, 20 instances of this nature have occurred, three to four weeks after the commencement of not very severe attacks. Kidney complications may occur as late as six weeks after the onset. Chronic renal disease is not infrequently caused by scarlet fever, and the possibility of this should always be kept in mind.

Klebs in 1876 divided the changes of the kidneys into three groups: "First in the febrile stage a granular desquamation of the epithelium; second, toward the end of the disease an acute interstitial nephritis with the kidneys large and lax, and on section smooth with grayish-white nodules, while microscopically the tubules are granular or fatty, with the tissue between infiltrated with lymphoid cells; third, during convalescence a glomerulonephritis."

The eyes are very rarely affected although occasionally there may be slight conjunctivitis. Hordeola, either external or internal, frequently occur, but do not give rise to any very serious trouble. A phlyctenular conjunctivitis or any chronic trouble with the eye is always exacerbated by an attack of scarlet fever.

The middle ear, particularly when the anginose symptoms are marked, frequently becomes actively inflamed. If the patient is seriously ill and delirious, this may be overlooked and not recognized until there is a profuse discharge from the meatus. In some instances the inflammation may be of a low grade without concomitant pain, and the membrana tympani will rupture without any symptoms referable to the ear. The percentage of otitis media in scarlet fever as given by different observers varies very considerably. Finlayson says that it was present in 10 per cent. of 4,397 cases observed by him. Caiger found otitis media in 11 per cent. of 4,015 cases of scarlet fever and Burckhart in 33 per cent. of his cases. At the South Department of the Boston City Hospital in 5,000 cases, 18 per cent. had middle ear trouble. When there are severe throat symptoms involvement of the middle ear may occur in 50 per cent. When this symptom appears early in the course of a severe attack the temperature does not seem to be specially influenced. Otitis media late in the course or during convalescence is always accompanied by a sharp rise in temperature and severe pain in the ear. In very young children persistent crying without apparent cause and a constant movement of the hand to the ear are indications of a commencing otitis media.

Welch and Schamberg in 18 cases of otitis media found that the discharge appeared on the following days: in 1 each on the 6th, 8th, 10th, 11th, 13th, 16th, 17th, 18th, 20th, 21st, 22d, 23d, 32d, and 35th days and in 2 each on the 9th and 19th days. At the South Department of 50 cases of middle-ear disease the days on which the discharge commenced were as follows: in 8 each on the 7th and 9th days, in 7 on the 5th day, in 4 on the 13th day, in 3 each on the 4th, 11th and 22d days, in 2 each on the 14th, 16th, 19th, 23d and 35th days, and in 1 each on the 20th, 32d, 38th and 40th day.

Cultures taken from the discharge in a comparatively small proportion showed the presence of the *Streptococcus pyogenes*. The most frequent organisms were the *Staphylococcus pyogenes aureus* and *citreus*. A profuse discharge from the ear and a slight amount of tenderness in the mastoid region indicate mastoiditis. A sudden rise in temperature, a cessation in

the discharge from the ear and even a limited amount of tenderness in the mastoid region also indicate mastoid inflammation. Bulging of the posterior wall of the meatus also indicates mastoiditis.

Blood.—The blood in scarlet fever has been carefully studied in reference to leukocytosis. Tileston and Locke[1] examined the blood in 35 cases of undoubted scarlet fever. Their conclusions are as follows:

1. "The blood of scarlatina in children differs from that in adults only in proportion to the differences in normal blood at the different ages.

2. "A slight secondary anæmia is the rule in all but the very mild cases, varying directly with the severity and duration of the disease. The fall in hæmoglobin is from 5 to 25 per cent. and in the erythrocytes from 100,000 to 700,000 per cmm. Both return to normal after a period of several weeks.

3. A leukocytosis almost invariably accompanies the disease and runs a characteristic course. Rising abruptly on the second to eighth day (18,000 to 40,000 per cmm.) the count falls rapidly for a few days, then more gradually to reach normal, in convalescence, usually at the end of from three to six weeks.

4. "During the period of invasion and eruption the polynuclear leukocytes are both relatively and absolutely increased, but decrease gradually with the fall in the leukocytosis till convalescence, when they may become relatively, though never absolutely, below normal. The mononuclears take an exactly opposite course. With the onset the eosinophiles disappear entirely or are greatly reduced, to rise above normal when defervescence begins. This eosinophilia persists until late convalescence. Myelocytes are often seen in small numbers, as in all infectious diseases.

5. "Complications, with a few exceptions, exert no influence upon the course of the blood. If severe they may increase the anæmia and in a few instances (nephritis and diphtheria) even produce a rise in the leukocytosis."

The results obtained in the examination of the blood in scarlet fever have not been productive of anything very definite so far as diagnosis and prognosis are concerned.

Sequelæ.—Kidneys.—Chronic disease of the kidneys is not an infrequent sequel, but it is not nearly so common as generally supposed. In an analysis of 5,000 cases of scarlet fever it was found that a chronic nephritis followed in 20 instances.

Heart.—Chronic heart disease sometimes follows, but the most serious trouble of this organ, as the result of scarlet fever, is the acute form. There are three types of scarlet fever hearts: first, where the heart is affected by the scarlatinal toxin; second, a condition of the organ due to nephritis, and third, secondary affections due to streptococcæmia. The heart is frequently dilated, and murmurs more or less persistent are common. In an analysis of 1,000 cases of scarlet fever a mitral systolic murmur was detected in 187 cases, gallop rhythm in 5, irregular action in 44, endocarditis in 3, and pericarditis in 5. A large proportion of these murmurs were due to dilatation.

In a second 1,000 cases studied with reference to heart complications during an epidemic of a somewhat severe type, the writer found a mitral systolic murmur in 432, gallop rhythm in 15, irregularity in 100, endocarditis in 10, and pericarditis in 8 cases. In a third 1,000 cases with a mild variety of disease, the figures were substantially the same as those in the first 1,000

[1] *Journal of Infectious Diseases*, vol. ii, No. 3, 1905.

cases. Although heart complications do occur during mild attacks of the disease, they are not nearly so common as during the severer attacks. Endocarditis and pericarditis, followed by dilatation and death, may occur.

Lymphatic Glands.—The lymphatic glands, more particularly those of the neck, are enlarged to a greater or less extent in nearly every case. Sometimes this is so slight as to escape detection. In other cases the glands assume the size of a pigeon's egg, are extremely hard to the touch and not necessarily tender. In a third class, the glands are enormously enlarged; there is a sharp rise in temperature, marked tenderness exists, and finally the glands suppurate. This condition may appear early in the course, or be postponed thirty-five or forty days from the commencement of the attack.

Cellulitis.—Cellulitis of the neck and other parts in the severer types of the disease is not infrequent.

Paronychia.—Paronychia is frequently observed, but as a rule, it is a late symptom and does not occur until desquamation is thoroughly established. This condition is due to infection with the pus cocci. Patients are constantly picking the dead skin from the fingers and in this way cause an abraded surface which allows the entrance of organisms.

Furuncles.—In a certain number of cases small boils form in various parts of the body and successive crops may appear.

Impetigo Contagiosa —Impetigo contagiosa is a not infrequent sequel. Sometimes the eruption may be so general as to be mistaken for varicella. During desquamation there are small abraded surfaces on the surface of the body which readily become infected with pus cocci from the finger-nails.

Pneumonia.—Pneumonia as a complication must always be considered in the severer types of the disease, although it is not very frequent. Bronchopneumonia occurs much more frequently than lobar pneumonia.

Pleuritis.—Pleuritis frequently occurs, and *empyema* may appear as an early or late complication. The condition is grave and frequently the immediate cause of death. When streptococci are found in the pus the condition is critical in the extreme.

General Peritonitis.—General peritonitis due to streptococcus infection as a complication is extremely rare; that it may exist and not be recognized is possible, for the patient may be so delirious as to prevent a diagnosis being made, or the prostration may mask the characteristic symptoms and render a diagnosis impossible. Among 5,000 cases of scarlet fever there has been a limited number with symptoms which suggested this complication, but the speedy subsidence of all symptoms and ultimate recovery would seem to prove that peritonitis could not have existed. In 4 out of 5,000 cases peritonitis did actually occur. In these the attack of scarlet fever was not especially severe and there was no cause for anxiety until the occurrence of the abdominal symptoms. This complication is exceedingly grave.

Arthritis.—This is not infrequent. There is sometimes marked effusion but this is rare and suppuration is still more infrequent.

Jaundice.—This was observed in 15 of 5,000 cases. It is not a symptom of any gravity and may occur at any time during the first three weeks of the attack.

Desquamation.—The desquamation commences in severe cases in four or five days from the beginning of the attack. In mild cases ten to fifteen days and sometimes twenty days elapse before the process begins. It may be very profuse or very slight, depending upon the brilliancy of the eruption

and the condition of the skin. Large scales of epidermis 1 to 2 centimeters square may be exfoliated. Children, as a rule, do not desquamate to such an extent as adults, because the skin is much more pliable and soft than in the latter. This is notable in the hands and feet. Every case of scarlet fever does not desquamate. This is particularly true of the extremely mild attacks of the disease. The desquamation has been described as lamellar, in distinction from that of measles, which is furfuraceous; but this is arbitrary, as a severe attack of measles may be followed by a lamellar desquamation, while that of a mild attack of scarlet fever may be furfuraceous. Desquamation commences, as a rule, in the axillæ and inguinal regions. Previous to this, however, if the fingers are carefully examined there will be found a white line at the junction of the pulp of the finger with the nail, looking very much as if a fine superficial incision had been made. This appearance cannot be seen unless a careful examination is made and the pulp of the finger is pulled away from the nail. This, of course, is commencing desquamation, but it can be seen before there is much, if any, general desquamation. This condition is often of great assistance in making a diagnosis after the disappearance of the eruption and before the general desquamation is apparent. Many outbreaks of scarlet fever have been traced to their source by appreciation of the significance of the condition just described. In adults this separation of the epidermis of the fingers is much more pronounced than in children, but it can always be demonstrated in the very young. In some instances the epidermis of the palms and of the soles separates in one large piece. Sometimes the process of desquamation leaves the skin extremely sensitive to heat and cold, and for this reason great care should be exercised in applying hot applications and embrocations to the skin of a patient in the desquamative stage. Neglect to appreciate the sensitive condition of the cutaneous surface in this stage has caused severe burns from hot applications the temperature of which would not have given rise to an injury in a person with a sound skin.

The process of primary desquamation is generally completed in five or six weeks; in rare instances eight weeks may elapse before the skin is in its normal condition. Secondary desquamation, by which is meant that exfoliation of the skin that sometimes, but not very frequently, occurs after the true desquamation is over, is ended in about ten weeks. The feet are the last portions of the body to desquamate.

Because a patient desquamates, it does not necessarily follow that he has had scarlet fever. All erythemata desquamate to a greater or less extent. Irritant applications will cause a certain amount of peeling, as is frequently seen on the hands. Some patients ill with scarlet fever do not desquamate to any very great extent; it therefore follows that too much stress in the posteruptive stage should not be placed on the presence or absence of this condition. Many individuals have been unjustly isolated on account of a desquamation that was in no way due to an attack of scarlet fever. Health authorities do not appreciate the fact that desquamation is not positive evidence of scarlet fever.

Relapse.—It is the generally conceived idea that one attack of scarlet fever absolutely protects the individual from a second; and while this may be true in a vast majority of cases, yet undoubted relapses do occur. This statement is made with the full understanding that the idea of an error in diagnosis must be combated. Second attacks of the disease occurring at intervals of

two and three years or longer are not so uncommon. It is important to distinguish a true relapse from a pseudorelapse. A re-infection must also be differentiated from a relapse. A true relapse occurs in from thirty to thirty-five days after the disappearance of the eruption. The usual symptoms appear at the onset. A pseudorelapse, or a *reversio eruptionis*, takes place just after the disappearance of the rash; sometimes it may appear in ten or as late as fifteen days after the subsidence of all symptoms. A re-infection may take place about fifty days after the eruption has faded. The recurrence of the disease, as a rule, is not accompanied with any very violent symptoms. An attack of so-called tonsillitis which is frequently noticed in the convalescent scarlet fever wards may possibly be a mild re-infection, as the appearance of the throat in these cases is very similar to that in scarlet fever. Thomas gives the following account of relapses among the crew of a British frigate: "The relapses among the crew of the frigate 'Agamemnon' occurred somewhat later than usual. According to Richardson, out of about 700 men, 300 were affected the first time so that the ship had to be cleared, thoroughly disinfected, and ventilated for more than one month. On April 4th it was again manned, and already, on April 9th, relapses occurred in 18 of the 102 convalescents who had returned to the ship; but the disease also recurred in many of those who had remained on land in the hospital, as also in 1 who had obtained furlough to return home. It is not reported how many days elapsed between the first and second attacks of the several cases; but as all the first attacks probably occurred in February, and the relapses in April, the interval evidently lasted much beyond one month in most cases. The second affection was either mild or as intense and characteristic as the first."

In the 5,000 cases of scarlet fever seen by the writer, relapses have occurred in 15 and second relapses in 5 cases. There have been 15 instances of re-infection occurring from forty to fifty days after the advent of the initial symptoms of the first attack. In 10 instances patients have been admitted with scarlet fever from two to four years after a first undoubted attack of the disease.

Diagnosis.—The diagnosis of a severe attack after the appearance of the eruption is not particularly difficult. In the preëruptive stage it is frequently extremely difficult and must be based upon the appearance of the throat, the peculiar redness of which is to be distinguished from the appearance in diphtheria. In a good light, puncta can be seen in the roof of the mouth, but must be differentiated from those sometimes seen in health. The appearance of the puncta in the mouth is similar to that on the skin, but there is a difference in the color, the former being of a more brilliant red than the latter. In this stage the appearance of the tongue is of great assistance. The history of vomiting is also an aid, as this is one of the most constant symptoms. Convulsions are frequently present in young children, and rigors in adults. The onset of the attack, as a rule, is sudden, but there may be a feeling of malaise for two or three days previous to pronounced symptoms. A sudden rise in temperature and an attack of vomiting should give warning and place the physician on guard. This is of particular importance in diphtheria wards and in wards where non-infectious diseases are treated. The temperature is generally elevated, but a patient may have an attack of scarlet fever with a perfectly characteristic eruption and only a slight rise in temperature throughout the whole course.

The diagnosis of a mild attack is frequently very difficult, but a careful examination of the throat and an appreciation of the peculiar appearance of the tongue will in most instances be sufficient. There are cases, however, in which the symptoms are so slight that it is impossible, no matter how much experience a man may have had, to decide definitely for or against the existence of scarlet fever. The only safe course is to isolate the patient for a certain length of time until he does or does not desquamate, although the absence of desquamation is not absolute proof that the patient has not had scarlet fever.

Measles.—This disease is sometimes mistaken for scarlet fever in the initial stage, but an examination for Koplik's sign and the coryza, with coughing and sneezing, ought to render this error extremely rare.

Scarlet Fever and Measles.—Scarlet fever and measles are not infrequently associated and diagnosis is extremely difficult. It is impossible to state definitely regarding the nature of the disease until the patient has been under observation for twenty-four to forty-eight hours. In this disease Koplik's sign and the condition of the conjunctivæ are to be taken into account, together with the appearance of the tongue and the accentuation of the eruption in the axillæ and in the inguinal regions. The presence or absence of eruption on the face and the mouth pallor are to be noted.

Rubella.—This disease, which very frequently serves as a cloak for either scarlet fever or measles, presents many difficulties in diagnosis. Sometimes the eruption is so fine as to resemble very closely that of scarlet fever. On the other hand, the small macules may simulate the commencing eruption of measles. Rubella is not nearly so common as is generally supposed, and many of the cases reported have been either scarlet fever or measles of a mild type. The glandular enlargement, on which so much stress is placed, is not of the slightest aid in differential diagnosis, as the same condition occurs in scarlet fever and measles. The writer has investigated a number of outbreaks of scarlet fever which were due to so-called attacks of rubella. In making a diagnosis of rubella, the physician ought to be absolutely sure of the nature of the disease. In doubtful cases, for the safety of the public, it is vastly better to isolate the patient for a few days rather than run the risk of an error and thereby cause an outbreak of scarlet fever. Too much emphasis cannot be laid on the fact that patients may have attacks of scarlet fever with very little constitutional disturbance, and this should influence the physician in making a diagnosis of scarlet fever in distinction from rubella.

Fourth Disease.—There has been a considerable amount of discussion during the past few years regarding a condition resembling scarlet fever to which this name has been given. While it is possible that there may be such a disease, it is much more reasonable to suppose that the eruption described was, in fact, that of a mild attack of scarlet fever. In the description of this disease Dukes[1] says:

1. "Although its resemblance is so close to scarlet fever in many features, it cannot possess any affinity with that disease, inasmuch as both diseases occurred concurrently in the same epidemic.
2. "Some of the sufferers had both diseases in the same epidemic.
3. "One patient had scarlet fever followed by the 'fourth disease'.
4. "Several had the 'fourth disease' followed by scarlet fever.

[1] *Lancet*, July 14, 1900.

5. "Although the 'fourth disease' has been confused with rose-rash and regarded as a mere variety of rubella, this conclusion is fallacious since nearly one-half the cases in an epidemic had already had rose-rash within a year or two, which, according to Cullen's established law, is incredible.

6. "I have purposely refrained from attaching a name to the disease in order to avoid the anomalous description of the same disease under an indefinite number of terms as in the case of its ally, which has been variously designated as 'rubeola notha,' 'rotheln,' 'rubella,' 'German measles,' 'epidemic roseola,' and 'rose-rash.'"

Dr. Dukes' points are not well taken; for instance, he said that some of the patients had the same disease in each epidemic, which might occur and very frequently does occur in epidemics of scarlet fever of a mild type. The stress that he lays upon Cullen's established law is altogether too great, as any one who has had any experience with infectious diseases knows. The question of relapses, to which allusion has already been made, proves that one attack of an infectious disease does not necessarily give immunity. From a somewhat extended experience in the diagnosis and treatment of the exanthemata, the writer can confidently state that, in his opinion, the existence of a "fourth disease" has not been proved, and that he has never seen just the condition which Dr. Dukes describes. Dr. Ker,[1] in an elaborate article on this subject, says: "Now, after eighteen months, and in the face of the able criticisms by the authorities on fever in children, I feel that only one verdict is possible regarding the contention of Dr. Dukes, and the verdict is a Scottish one,—'not proven.'"

Among the 24,000 patients, the majority of whom were children, treated at the South Department of the Boston City Hospital during the past ten years, no such eruption as that described by Dr. Dukes has been observed. During this time there has been an immense number of anomalous eruptions not belonging to the exanthemata and also many anomalous types of the exanthemata, but no condition worthy of the name of "fourth disease" has been noticed. The writer cannot help feeling that, although the discussion regarding the "fourth disease" may possibly have done some good in causing the more careful examination of patients with eruptions and, consequently, a more accurate diagnosis, still on the other hand it has probably increased the prevalence of scarlet fever on account of incorrect diagnosis.

Erythema Infectiosum.—Escherich has described under this name an exanthem which may possibly be mistaken for scarlet fever, but the eruption is more macular than punctate, and the absence of throat symptoms and the appearance of the tongue ought to make the diagnosis comparatively easy. Stricker described in 1899 an epidemic of "Die neue Kinderseuche in der Ungebung vom Giessen, erythema infectiosum." This disease is probably the same as that described by Escherich. Tripker, in Coblenz, in 1901 described a similar disease. Plachte in 1904 also described this disease. Several other observers have also mentioned the existence of this exanthem. The writer has observed several cases of this nature. This disease is also frequently mistaken for measles, but in the cases that came under the observation of the writer, although the patients were not isolated, no cases of scarlet fever or of measles were contracted from them. That this disease is an entity cannot be disputed, and it is important from a diagnostic point of view, as all of the patients who had this eruption applied for admission to the

[1] *Practitioner*, February, 1902.

scarlet fever wards or to the measles ward of the South Department. It is needless to say that they were refused admission. They were, however, carefully watched for some considerable time in order to verify the diagnosis. Desquamation to a limited extent was present in most of the cases, but it was not so general as in the case of scarlet fever. The absence of throat symptoms, the fact that the papillæ of the tongue were not enlarged, and the pronounced eruption on the face, were the principal points on which the diagnosis was based.

Lichen Tropicus.—This disease is frequently mistaken for scarlet fever, and when there is a rise in temperature, as not infrequently occurs in children, the diagnosis is somewhat difficult. If attention is paid to the condition of the throat, the peculiar appearance of the tongue, and to the fact that in scarlet fever the eruption is accentuated in the axillæ and in the groins, while in lichen tropicus it is not, a correct diagnosis can be made.

Drug Eruptions.—Many drugs cause the appearance of a punctate erythema which it is frequently very difficult to differentiate from that of scarlet fever if the diagnosis is to be made simply from the condition of the skin. In all of these the diagnosis must be based upon the condition of the mucous membrane of the throat and on the appearance of the papillæ of the tongue, together with the constitutional disturbance. The appearance of the throat and the enlargement of the papillæ of the tongue have already been described.

Quinine in certain individuals will cause a very general eruption, punctate in character, which simulates that of scarlet fever to a remarkable degree. There is, however, no congestion of the throat and no enlargement of the papillæ of the tongue. Profuse desquamation follows this eruption which can in no way be distinguished from that of scarlet fever. It is lamellar in character, and frequently large scales of epidermis will be exfoliated from the palms and soles. In malarial fever after the chill, during the remission when quinine is administered, this eruption not infrequently occurs. As there is marked constitutional disturbance at this time, no assistance in the differential diagnosis can be obtained from this condition. It is at this time that the condition of the mucous membrane of the mouth is of the greatest help in arriving at correct conclusions.

Strychnine in small doses sometimes, although rarely, causes a punctate erythema resembling that of scarlet fever.

Atropine causes an eruption which, from its resemblance to that of scarlet fever, caused the idea to be prevalent a few years ago that this drug was of advantage in the treatment of the disease. The dilatation of the pupils, the dryness of the fauces, the peculiar blush on the face, are the important points on which to base the differential diagnosis. It is remarkable how small an amount of atropine will sometimes cause an eruption. The writer has seen several cases where atropia, used for mydriatic purposes, caused an eruption which was incorrectly diagnosed as that of scarlet fever.

Corrosive sublimate, when used for sterilization for an operation, will sometimes cause a punctate erythema twenty-four hours after its application. The constitutional disturbance following the operation and the nausea and vomiting caused by the ether render the diagnosis more difficult. In this condition the mucous membrane of the mouth is the only guide to a correct diagnosis.

Iodoform, even in very small quantities, may cause an eruption similar to that of scarlet fever. From the appearance of the eruption alone a diagnosis is impossible; the determining factor is the mucous membrane of the mouth.

The eruption caused by copaiba, although more frequently resembling that of measles, may sometimes have a punctate appearance like that of scarlet fever.

Allusion has been made to the fact that hemorrhagic smallpox is sometimes mistaken for scarlet fever, and *vice versa*. The preliminary rash of smallpox sometimes bears a slight resemblance to that of scarlet fever, but if the patient is carefully examined from head to foot a few papules of smallpox can generally be detected. Vesicles can frequently be seen in the mouth at the same time.

In a severe attack of chickenpox where the eruption is very abundant, the interspaces between the vesicles present a punctate appearance which has led to an error in diagnosis. When the two diseases are associated, as they not infrequently are, the skin has an entirely different appearance from the one just described.

In short, in making a diagnosis of scarlet fever the whole clinical picture must be taken into account, but the chief reliance must be placed on the condition of the mucous membrane of the mouth.

The history of exposure is always a weak staff on which to lean, and probably has caused many errors of diagnosis. The statements in the foregoing paragraphs are not theoretical in their nature, but are the result of careful and anxious study at the bedside of the patient. Although these statements may be doubted by those who have had a limited experience with scarlet fever, the writer is thoroughly convinced that they are correct.

"Surgical Scarlet Fever."—The existence of this in distinction from medical scarlet fever is a disputed point, but we are of the opinion that there is no such disease. Patients on whom a surgical operation has been performed, if exposed to scarlet fever, are no doubt more likely to contract the disease because the operation diminishes their resisting powers, but this does not constitute a distinct form of scarlet fever. Before the days of aseptic surgery, when septic rashes were more common than at the present time, much more was heard regarding surgical scarlet fever.

Patients who have burns of either the first or second degree, if exposed to scarlet fever, may contract the disease more readily than if the skin is intact, but this is not surgical scarlet fever; it is scarlet fever in the wounded. Considering the great frequency of burns and the prevalence of scarlet fever, it is remarkable that scarlet fever is not more often contracted by children with burns.

An individual who has had repeated attacks of appendicitis may have the inflammation excited in that situation by the initial symptoms of scarlet fever. The nausea and vomiting attendant on the onset of the disease may lead the surgeon to decide on an operation. Twenty-four or forty-eight hours later an eruption of scarlet fever appears. This is not surgical scarlet fever but scarlet fever in the wounded. Several such instances have been observed by the writer. In these cases investigation proved that there had been a direct exposure to scarlet fever a short time previous to the operation.

Prophylaxis.—The segregation for a long time of patients ill with scarlet fever is the only method of preventing the prevalence of the disease. In smallpox we have an efficient aid in vaccination. In diphtheria, antitoxin

limits the spread of the disease, but in scarlet fever, in the light of our present knowledge, we must depend upon isolation, preferably in special hospitals. In a tenement house it is very difficult and well-nigh impossible to properly isolate a patient.

The medical inspection of schools, if properly conducted, would be an efficient means of limiting the spread of scarlet fever. It is an undeniable fact that walking cases are responsible for many outbreaks. As scarlet fever is infectious from the initial vomiting until desquamation is completed, it is evident that isolation should be early and continue for a long time. It has been stated by some observers that scarlet fever cannot be communicated before the appearance of the eruption, but this is not correct, as a child may communicate scarlet fever during the initial stage of vomiting and sore throat. This has been proved by experience in many instances. While we have no definite knowledge, so far as bacteriology is concerned, regarding the infectiousness of the desquamative stage, there is abundant clinical proof that the epidermic scales have the power of communicating the disease.

Discharges from the nose and from the ears of a convalescent scarlet fever patient are undoubtedly infectious. It therefore follows that in order to accomplish anything in limiting the spread of scarlet fever isolation must be early, rigidly enforced, and continued for a long time. As the poison of scarlet fever remains active for a long time and can be conveyed by fomites, it is very important that the clothing worn by the patient at the time he was taken ill should be thoroughly disinfected. The neglect of this precaution has caused outbreaks of the disease. It is necessary to be absolutely sure that disinfection is effectual, and, in order to accomplish this, the details must be carefully carried out. Much disinfection is useless because carelessly done, and therefore the results are not satisfactory.

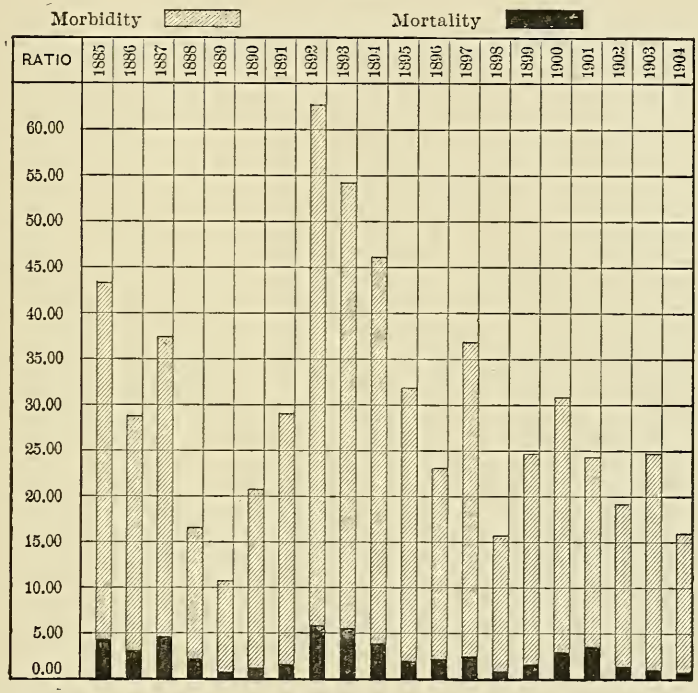
The establishment of sanitary wash-houses to which the clothing and bed-linen of a patient ill with scarlet fever could be sent to be thoroughly disinfected and washed would be an important factor in limiting the spread of the disease. Glasgow, the sanitary arrangements of which are second to no city in the world, has a large building devoted to this purpose, and in this way much has been accomplished.

Isolation hospitals are the most effectual means for diminishing the spread of infectious diseases in crowded cities. Glasgow has probably suffered more in this respect than any other city, and it was not until a special hospital for the treatment of these diseases was established that there was any marked diminution either in the mortality or morbidity of scarlet fever. The effect of the first municipal fever hospital in Glasgow, opened in 1865, was so marked in diminishing the death-rate from scarlet fever that a second hospital was opened in 1870. The health authorities, not satisfied with these accommodations, because they were unable at certain times of the year to give each patient 2,000 cubic feet of air space, and because they were unable to vacate certain wards for six months for disinfection and renovation, decided to purchase land for a third fever hospital, which was opened in 1900. This hospital will accommodate about 500 cases, giving 2,000 cubic feet of air space to each patient. It is not exclusively for scarlet fever patients, but also for other infectious diseases. There is a sanitary wash-house connected with it for the use of patients isolated at their homes. About 60 per cent. of all cases of scarlet fever occurring in Glasgow are treated in hospital. In this

city there are beds, for patients ill with infectious diseases, for 9.79 out of every 10,000 of the population.

In London the first hospital for infectious diseases under the charge of the Metropolitan Asylums Board was opened in 1871. At present there are nine of these hospitals and one large convalescent home. The ratio of hospital accommodations for infectious disease is 9 per 10,000 population. About 58 per cent. of cases of scarlet fever are treated in hospitals in London. Previous to 1888 in Boston there was no special provision for the care of patients ill with scarlet fever and in 1887 it was decided by the Trustees of the Boston City Hospital to erect a pavilion for this purpose. At first there were comparatively few applications for admission; but as time went on the public generally began to realize the advantage of sending patients to the hospital.

FIG. 39.



Ratio of morbidity and ratio of mortality of scarlet fever in Boston per 10,000 of the population from 1885 to 1904, inclusive.

After a time this ward became crowded, so that many applicants were refused admission. In 1892 it was decided to erect a large hospital for infectious diseases, particularly scarlet fever and diphtheria, which was opened in 1895. The effect on the morbidity ratio and mortality ratio of scarlet fever since the establishment of this hospital is shown in Fig. 39. It will be seen that since 1895 the prevalence of the disease has diminished to a very considerable extent and that the mortality ratio has also diminished. The average ratio of morbidity of scarlet fever from 1885 to 1894 was 34.84, while that from 1895 to 1904 was 24.68—a very considerable diminution.

The mortality rate for the first period was 2.99, while that for the second period was 1.91. A large proportion of the patients in Boston who are seriously ill with scarlet fever are sent to the hospital, but those who have the milder attacks are not isolated and therefore serve as potent factors in causing its spread. Notwithstanding this fact, it seems that the isolation hospital in Boston has accomplished a satisfactory result in lessening the prevalence of scarlet fever. About 40 per cent. of the reported cases of scarlet fever in Boston are treated in the hospital.

Compulsory notification of scarlet fever originated in England quite a number of years ago, and for a time was bitterly opposed not only by the laity but also by physicians. It was claimed that it interfered with private rights and was a source of annoyance to the individual. After much discussion the Compulsory Notification Act was passed in England, and since that time it has been generally adopted by local boards of health in this country. This regulation has accomplished much in the suppression of infectious diseases, but it is evaded in many ways.

The length of time that a patient ill with scarlet fever should be isolated has been the subject of careful study. The practice in different countries varies very considerably, as, for instance, in Glasgow the time is much longer than in England and in this country. Some physicians go so far as to say that the desquamation is not infectious, but that the contagium of scarlet fever is in the discharge from the mucous membranes. This is a little too radical an opinion, and is not in accordance with clinical experience. There is no doubt that during the active stage of primary desquamation scarlet fever is infectious. There is very grave doubt if the secondary desquamation is infectious.

A second case appearing in a family shortly after the discharge of a patient from the scarlet fever wards is always a source of annoyance and frequently gives rise to unjust criticism. It is very doubtful if a patient who has been in a hospital fifty days, who has had innumerable baths and a disinfecting bath of corrosive sublimate 1 to 10,000, can communicate the disease. Many of these so-called "return cases" have been investigated by the writer, and it has been found that there was an intermediate case and sometimes two, so mild in their nature as not to attract attention, and that these were the cause of the outbreak of the disease, and not the patient who was discharged from the hospital. In institutions, where children as a rule are more carefully watched for eruptions than in private families, it has been our experience that so-called return cases never occur.

At the South Department the average length of time that a patient remains in the hospital is fifty days. No patient who has a discharge from the nose or an abnormal condition of the throat leaves the hospital. Of 3,000 patients discharged from the scarlet fever wards, there was a percentage of 1.74 of alleged return cases. Investigation failed to show anything abnormal in the condition of the individuals who were supposed to be the cause of the alleged return cases.

In 1898 the Metropolitan Asylums Board of London commenced a series of investigations on this point, made by Simpson[1] and carefully conducted for six months. His report was referred to a committee of the Royal College of Physicians, London. The conclusions reached were as follows:

[1] Metropolitan Asylums Board—London, *Annual Report*, 1903.

"The committee are impressed with the small percentage of those cases which, on investigation, were found to give rise to fresh infection, *viz.*, 1.1 per cent. of the total cases discharged from hospital of diphtheria and scarlet fever taken together. They also note that of these no fewer than 80 per cent. were suffering from some mucous discharge, either during their stay in hospital or shortly subsequent to their return home.

"The total number of return cases of scarlet fever was 90, giving a percentage of 1.3 of the total number discharged. In endeavoring to arrive at a definite conclusion as to the necessary length of detention in scarlet fever, there are two points on which elucidation is required, the degree of infectivity attaching to (*a*) the desquamation of the skin and (*b*) any mucous discharge occurring during convalescence.

"In respect of the infectivity of the later desquamation of the skin in scarlet fever, it is to be observed in Dr. Simpson's investigation that in only 2.7 per cent. was there any reason to suspect desquamation of the skin as the cause of secondary infection. The relatively high degree of infectivity of the mucous discharges, as compared with the later desquamation of the skin in scarlet fever, as shown in the report, is one which is obtaining an increasing support among those of the profession who have had much to do with infectious diseases. It would suggest that possibly too much importance has been hitherto attached to the infectivity of the skin during the later weeks of scarlatinal convalescence. The committee have communicated with the authorities of many hospitals in other large cities in this country, in America, and in Germany, and have ascertained that the period of detention insisted on is of somewhat shorter duration than is practiced in those of the Metropolitan Asylums Board. Unfortunately no corresponding record of the incidents of return cases is available for comparison with that recently obtained for the Metropolitan Asylums Board."

In many instances the alleged return cases of scarlet fever have no connection with the discharged patient. It is not an infrequent occurrence for a child to be admitted to the scarlet fever wards a few hours before his brother or sister is discharged. If these discharged patients had arrived at their homes twenty-four or forty-eight hours earlier, as in many instances they would, if the parents had come for them as soon as notified, the second cases would have been considered return cases. It is also a significant fact that in the majority of the return cases the patients are of the school age and, therefore, the possibility of infection other than that of the patient who has been discharged is very great. That the clothing worn by the patient when he was taken ill and which was packed away during the stay in hospital may be a source of infection is extremely probable.

Lauder,[1] who takes a very decided stand regarding the infectivity of discharges from the mucous membranes and does not place so much stress upon the contagiousness of the desquamation, says that in 1902 no cases of scarlet fever were discharged from the hospital until all peeling had ceased, but that during 1903 he has acted on the belief that the infection is in the respiratory tract, that the constitutional condition, and particularly the rash, are only the result of toxic products, and that, therefore, the desquamation of the skin is not *per se* a source of danger.

He gives the following tables:

[1] *Lancet*, March 12, 1904.

Table I.

Year.	Cases Notified.	Removed to Hospital.	Discharged from Hospital.	Average Period in Hospital.	No. Causing "Return" Cases.	Cases Treated at Home.
1902	261	208	164	48 days	7	53
1903	427	353	325	34 days	7	74

Table II.

	Discharged.	Average Duration in Hospital.	No. Causing "Return" Cases.
1. Without peeling or complications.....	33	33	0
2. Peeling without complications.....	204	28	2
3. Cases with complications.....	88	50	5
Total.....	325	34	7

These tables show that in 1902 the average period of detention in the hospital was forty-eight days, while in 1903 it was thirty-four days. In 1902 there were 208 patients admitted to the hospital, and there were 7 instances of return cases, while in 1903 there were 353 cases admitted and 7 instances of return cases. It is interesting to note that there were no return cases when there was no peeling or complications; that when there was peeling without complications there were 2 instances of return cases; that when there were cases with complications there were 5 instances of return cases.

It therefore seems evident, first, that discharges from mucous membranes in scarlet fever are infectious; second, that the desquamation is also infectious. As a corollary to the foregoing conclusions it may be said that no patient should be removed from isolation as long as there is any discharge from the mucous surfaces or as long as there is primary desquamation. There can be no definite time limit, but the average in the majority of cases from the commencement of the initial fever until the process of desquamation is completed is about fifty days. In certain rare instances, particularly in very young children, the time may be somewhat less.

It is extremely doubtful if cows are susceptible to scarlet fever, but the possibility of milk becoming infected with the germs of the disease from the hands of a dairyman who has a mild attack of scarlet fever must be conceded. Too many epidemics have been traced to infected milk to doubt this. It is, therefore, incumbent on health authorities when an outbreak of scarlet fever occurs to carefully examine the dairyman and all persons who are brought in contact with milk. In London the medical supervision of milk farms is very carefully conducted. In this country it would be well, for the health of the community, if the example of London was followed.

Infectiousness of Scarlet Fever.—While scarlet fever is extremely infectious, the degree of infectiousness is not so great as that of the other

exanthemata. Smallpox in the unvaccinated is the most infectious of all diseases; then in order comes measles, and next scarlet fever. The length of time of exposure necessary to contract the disease may be very short, as cases are on record, the accuracy of which cannot be doubted, in which the time of exposure could not have been more than one-half hour. Several have been observed by the writer in which the time of exposure varied from an hour to an hour and one-half. In these instances, although the patients who contracted the disease were in the same room with cases of scarlet fever, they were not in immediate contact; that is to say, they did not occupy the same bed and were some eight or nine feet from the scarlet fever patient.

Prognosis.—The prognosis depends very considerably on the complications and not on the disease itself, except in the fulminating type. In a moderately severe attack, provided there are no complications, the prognosis is favorable. It is remarkable how seriously ill a patient may be for four or five days and how rapidly at the end of this time he will commence to improve. On the other hand a patient with an apparently mild attack, if there are complications, may succumb to the disease very suddenly. The physician should always have in mind the possibility of nephritis, the dangers of endocarditis and pericarditis, the chances of a bronchopneumonia, the possible occurrence of an empyema or mastoiditis; and it therefore behooves him to give a guarded prognosis in every case, be it mild or severe.

Meningitis occurs very rarely as autopsies have shown, but a condition suggestive of meningitis does not infrequently occur. This is exceedingly serious and should always suggest an unfavorable prognosis. Few patients with meningitic symptoms recover.

Uræmic convulsions are always a cause for apprehension. About 50 per cent. of patients in this condition succumb.

Empyema is a very serious complication. Only a small proportion recover, and in those who do convalescence is extremely tedious. Bronchopneumonia and, in a certain number of cases, lobar pneumonia are responsible for about 22 per cent. of deaths; it therefore follows that lung complications are of great significance.

Endocarditis and pericarditis, particularly pericarditis, are of the gravest import, and their existence is tantamount to the death of the patient. Heart murmurs, if hæmic in their nature, are of no particular significance so far as recovery is concerned. Chronic heart disease is not uncommonly a result of an attack of scarlet fever.

Mastoiditis, if not relieved by an early operation, may cause death by extension of the inflammation to the brain.

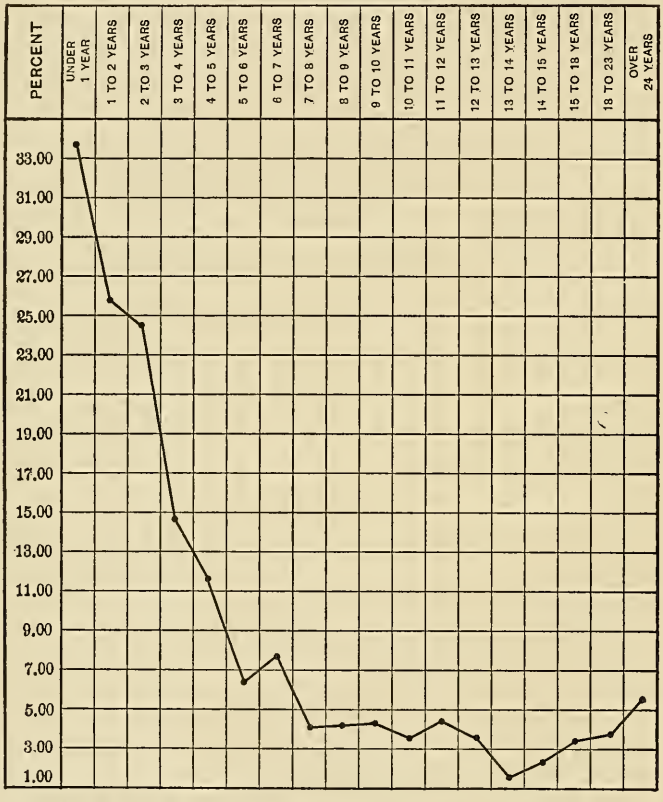
Age is an important factor in influencing the prognosis. The percentage of mortality in very young children is high (Fig. 40). It will be seen that under one year of age the mortality was 33 per cent. and from five to six years of age it was only 6 per cent. The lowest rate, 1 per cent., occurred in patients from thirteen to fourteen years of age.

Scarlet fever occurring in the course of acute diseases and in patients on whom a surgical operation has been performed is sufficient reason for a grave prognosis A woman in the puerperal state, if she contracts scarlet fever, is always in a serious condition.

As epidemics vary in severity no definite rules can be given regarding prognosis. Each case must be judged on its merits. The mortality varies in different epidemics from 4 to 15 with an average of 8.42 per cent. This rate

is estimated on 37,810 cases in Boston during the past twenty-eight years. Johannsen gives the mortality in Norway in 84,580 cases as 14.17 per cent. Caiger gives the mortality of 81,350 cases treated in the hospitals of the Metropolitan Asylums Board of London as 8 per cent. The death-rate in the Municipal Hospital of Philadelphia from 1891 to 1902 in 5,213 cases was 9.72 per cent. At the South Department of the Boston City Hospital the death-rate in 5,000 cases was 9.28 per cent.

Fig. 40.



The percentage of mortality by age in 5,000 cases of scarlet fever.

Treatment.—This is both hygienic and medical. The hygienic treatment is simple. It consists in placing the patient in a well-ventilated apartment from which all hangings and upholstered furniture have been removed. Isolation, on which too much stress cannot be placed, must be rigid. Only two persons should have the immediate care of the patient,—the day nurse and the night nurse. The physician when making his visits should wear a gown and a cap. After the visit he should be careful to wash his face and hands in a solution of corrosive sublimate. The nurses should be careful to change their clothing when they leave the patient and come in contact with other persons. The room should not be overheated, as a high temperature renders the patient much more uncomfortable even in a mild

attack. The temperature should never exceed 65° F. in cold weather. In warm weather it is frequently impossible to keep the temperature at this point. The diet should be bland; milk for the first two or three weeks of the illness is the most desirable article. The patient, if there is no nausea, should be induced to drink a large amount of water. Cracked ice and ice-cream, particularly if the anginose symptoms are pronounced, are frequently very grateful. The bedclothing should be light, as there is nothing that contributes so much to discomfort as heavy coverings. There is very little danger of contracting a cold during an attack of scarlet fever. The popular idea that by causing perspiration the eruption will become more brilliant is incorrect. Recession of the eruption, although it sometimes occurs, is not caused by cold, but is a part of the natural history of the disease. In short, the hygienic treatment may be summed up in these words: Make the patient as comfortable as possible by cooling drinks and a cool, well-ventilated apartment.

The medical treatment must be symptomatic. The different phases of the disease must be carefully watched and untoward symptoms alleviated by the proper remedies. There is no known drug that has a specific action. In the mild cases no medication is required. If there is marked prostration, alcohol can be administered in large doses but routine treatment by alcoholic stimulation is to be reprobated. Strychnine is a good stimulant in certain cases and children, as a rule, bear it very well. The dose according to age is given in the chapter on diphtheria.

If there is marked delirium, morphia in small doses, according to the age of the patient, can be used with marked benefit. It must be borne in mind that children do not bear morphia well, and it should be administered with the utmost caution.

The bowels should be kept open by mild laxatives. Compound licorice powder is a very good preparation. Calomel in small and divided doses is often of great advantage.

Irritant diuretics should never be used, as the kidneys are always congested to a greater or less extent. The less that is done in the direct treatment of the kidneys by diuretics the better for the patient. The patient should have large amounts of water. Flaxseed tea will sometimes be more agreeable than water. Orange flower water is a good preparation. Barley water may also be taken. Weak cream of tartar water is frequently very grateful.

If there is swelling of the cervical glands, ice-collars are frequently of marked benefit, but they must not be continued for too long a time. As soon as there is a suspicion of fluctuation, incision should be made. Poultices are of doubtful advantage previous to incision and of no use after the pus has been evacuated. In the treatment of cervical adenitis, while it is important to have a sufficiently large opening for proper drainage, it is well to bear in mind that an unnecessarily long incision causes an unsightly scar.

Digitalis, if there is no dilatation of the heart and its action is weak, may be administered with satisfactory results, but it should be given with the utmost care, as in certain cases it may do more harm than good.

Hydrotherapy is an efficient method in the treatment of scarlet fever. It reduces the temperature and calms the delirium. When the temperature is above 103° F. sponging with water at a temperature of 85° F. is frequently of great use. Immersion in a bath-tub with the water at 85° F. may also be used. Children, as a rule, however, bear sponging better than tub baths.

If the patient bears sponging well, and if the temperature is reduced two or three degrees by it, the prognosis is favorable; if, however, the sponging causes a chill, and the temperature is not reduced, it is better to omit it. An ice-cap should always be placed on the head of the patient during the sponge bath. In patients with a full, strong, bounding pulse and an active delirium, the fan bath is often of great use; the patient is wrapped in one layer of gauze and the body is then sprinkled with water at a temperature of about 90° F. A nurse stands on each side of the patient and fans him vigorously for ten or fifteen minutes. The fanning causes the rapid evaporation of the water and the temperature is reduced in a marked degree. The ice-cap should always be applied in these cases. The pulse should be carefully watched. In some instances the water may be of a lower temperature. While sponging and the tub bath are of undoubted advantage in many cases, there are instances in which this treatment does not seem to be beneficial. Routine practice in the treatment of any disease is not to be advised. The conditions must be carefully studied in each individual case, and the adoption of this line of treatment must be left to the judgment and good sense of the practitioner.

The milk pack is sometimes of use. A sheet is saturated with milk and the body of the patient is wrapped in it, only one layer of cloth being over the surface of the body. He is then allowed to remain in this pack for ten or fifteen minutes. The body should not be wiped dry, but the moisture allowed to evaporate. A cold water pack can be administered in the same way, and frequently is more beneficial than either the sponge bath or the tub bath. It is well before giving either the baths or the pack to administer some alcohol.

Inunction with cold cream or cocoa butter will sometimes reduce the temperature to a certain extent. Vaseline is not adapted for this purpose and cocoa butter is the best agent to use. In private practice, during the process of desquamation, inunction is advisable, because it limits the number of scales of epidermis that would float in the air and diminishes the possibility of infection. The addition of carbolic acid to the substances used for inunction does not do any good and, when we take into account the actively absorbent condition of the skin in scarlet fever, it may cause poisoning. Cases are on record where a very small amount of carbolic acid in cold cream used for inunction has been followed by very serious symptoms.

Placing the patient in a cold room at a temperature of 58° F. with very little bedclothing has been advised. The writer has seen satisfactory results from this method of treatment, but it cannot be recommended as routine practice. Antipyretics are of doubtful advantage. In an adult with a full bounding pulse and a high temperature, phenacetine may be of benefit but must be administered with care. In children it is to be absolutely prohibited. Quinine in large doses is of no benefit.

Throat.—If the attack is complicated by diphtheria, antitoxin should always be administered in substantial doses. There is no danger of causing trouble with the kidneys by the use of the serum. If the anginose symptoms are comparatively mild, irrigating the throat with a weak Dobell's solution or a solution of boric acid contributes to the comfort. Children will not use gargles and sprays frighten them. When the anginose symptoms are pronounced, spraying the throat with diluted peroxide of hydrogen, if it can be accomplished without too much resistance on the part of the patient, may be advised. Direct applications to the throat by a swab saturated with Loeffler's

iron toluol solution is of benefit. The swab should be held in contact with the diseased parts for a short time. Irrigation of the throat with a solution of corrosive sublimate 1 to 8,000, or with a solution of permanganate of potash 1 to 2,000, can be used. When there are small gangrenous patches in the throat, tincture of iodine may be applied.

Noma.—Noma occurs rarely in the course of scarlet fever, but is a complication of very great severity. Curetting and the application of fuming nitric acid may be of use. If the process extends, excision may be tried, but the possibility of its doing any good is very slight.

Purulent Rhinitis.—If there is a profuse discharge from the nose, cleansing with swabs of absorbent cotton and the insufflation of calomel are the best methods of treatment. Irrigation of the nose, on account of the danger of causing middle-ear disease, cannot be too strongly deprecated.

Ears.—The ears should receive careful attention during the whole course. It is not sufficient to wait for the development of symptoms but the ears should be carefully examined every two or three days to see if there is anything abnormal in the appearance of the membrane.

G. A. Leland describes three varieties of middle-ear disease occurring in the course of scarlet fever, and gives the following directions for incision of the drum-head:

"First, the regular sthenic variety, in which the drum-head is red, somewhat thickened, with the lustre abolished and the contiguous canal of the same appearance This is accompanied by extreme pain; the onset is sudden and the bulging occurs early. Incision of the drum-head should be very free, beginning in the lower inferior quadrant, midway between the umbo and the posterior wall, extending upward three-quarters of the distance to the posterior fold and then backward to come out on the external canal. When the discharge is sufficiently copious to keep the incision open, there will probably be little trouble, but when the incision closes there will be subsequent earaches which will necessitate secondary operations.

"Second, there is a variety of middle-ear involvement which is not characterized by pain, especially in children and where the only warning that the ears are affected is a rise in temperature. The examination of the ears will reveal a drum-head which may or may not be bulging, but which has a macerated look. It is thickened, lustreless, the landmarks can only be faintly distinguished, the light reflex is absent, and there is only a slight redness of the contiguous wall of the bony canal. If perforation has not taken place a free incision should be made for the sake of drainage not only of the tympanic cavity but for local depletion of the membrane itself, and also, which is to be considered a very important point, to insure that the perforation shall be at the point of election, namely, the posterior inferior quadrant. Although this variety of drum-head may be pathologically perforated without suffering, it is the better practice to incise it in order to limit destruction as much as possible.

"Third, this variety of middle-ear disease is sub-acute, the drum-head is more or less transparent and pinkish in color. The tympanic plexus of vessels are very markedly filled, streaking down over the membrana flaccida into the swollen postmanubrial vessels. There is more or less effusion present in the cavity. This condition frequently occurs without pain in children, and in adults with only a transient earache. There is always a slight rise in temperature.

"Incision of the drum-head may be described as follows: Special attention being drawn to antisepsis, the avoidance of unnecessary destruction and to the after care, the auricle and contiguous skin of the scalp and face should be thoroughly washed. The external canal should be thoroughly washed by cotton on an applicator, and a solution of corrosive sublimate, 1 to 1,000, which may be allowed to remain in the canal for fifteen or twenty minutes and then removed with sterile wicks. Then with a spear-shaped paracentesis needle, or a slightly curved bistoury previously soaked in a saturated solution of boracic acid in alcohol and allowed to dry, which materially assists the vision in the introduction of the sterilized blade into the small external canal, the puncture should be made in the lower part of the posterior segment of the drum-head, which is almost without exception the most prominent part, and carried through the membrane only.

"In the third variety just mentioned a small cut through the lower two-thirds of the posterior half of the drum-head will be sufficient. In the other two varieties a large incision is indicated. After introducing the point of the instrument it should be carried upward and outward two-thirds of the extent of the membrana tympani and then backward to the posterior wall, care being taken to withdraw the point outward far enough to avoid the incudo-stapedial joint and yet to completely divide the membrane itself. In the second variety the membrane being thickened gives the feeling of cutting through something having considerable resistance; like the skin of an orange.

"The treatment after incision should be carried out with strict attention to surgical cleanliness, and to this end a wick of sterile or corrosive sublimate cotton is introduced gently into the canal to assist the exit of the discharge by capillary attraction. On the outside of the wick a pad of the same cotton should be placed and changed as soon as it becomes wet, the wick being changed once or twice in twenty-four hours according to the amount of the discharge. Instillation of corrosive sublimate, one part to three or four thousand, may be made to sterilize the external canal and render it less liable to secondary infection which, in the form of localized furunculosis, may give the patient considerable suffering. As long as the discharge continues free the incision requires no attention, but if the discharge diminishes or stops and there is a rise in temperature and pain a second incision should be made.

"In struggling children, in order to insure accuracy, a few whiffs of ether or of chloroform sufficient to cause early primary anæsthesia are of great assistance."

If there is pain and tenderness in the mastoid region, the Leiter coil or the Sprague ear ice-bag should be applied. If there is not relief at the end of forty-eight hours this treatment should be omitted. The continued use of the ice-bag will mask the symptoms so that a dangerous condition may supervene without proper warning. An early operation is to be advised in inflammation of the mastoid cells. The condition of the patient is rendered hazardous by waiting until there is marked swelling behind the ear and a great amount of tenderness. A long continued profuse discharge from the meatus without any tenderness behind the ear is an indication for the mastoid operation not only for the relief of this symptom but in order that the hearing of the patient may be saved.

The choice of the operation must be made in each individual case, based on the condition of the patient. An early operation has been advised in each

case occurring at the South Department of the Boston City Hospital and the results have been satisfactory, no death having occurred in sixty operations.

Nephritis.—Absolute rest in bed is imperative; the diet should be restricted, the bowels receive attention, and warm baths given. Allusion has been made to the importance of forcing liquids as a part of the routine treatment. Fomentations over the region of the kidneys are frequently of benefit. When there are twitchings of the muscles, delirium and stupor, a hot pack or a warm bath should be given. A warm bath is perhaps more satisfactory. Vapor baths are of advantage but the hot air bath very rarely does any good. The pack can be given in the following way: The patient is wrapped in a blanket which has been wrung out of water at a temperature of 100° F. A dry blanket is placed over this and then the patient is covered with rubber cloth. The patient should have an ice-cap applied during the time that he is in the pack. It must be borne in mind that the skin of a patient ill with scarlet fever is extremely sensitive to heat, and therefore care must be exercised not to have the temperature of the water above 100° F. If convulsions supervene, resort must be had to ether carefully administered. Pilocarpine is of doubtful advantage and should rarely be given to children. Nitroglycerine in rare instances, in doses of gr. $\frac{1}{300}$, may sometimes be of use. A saline infusion is frequently followed by a relief of the symptoms. The intravenous injection of salt solution has sometimes been followed by satisfactory results. Venesection has been advised previous to the intravenous injection. It is doubtful how much good hydrate of chloral, by the mouth or by the rectum, has accomplished in the convulsive seizure. The writer has not seen any advantage from its use in children. Morphia in small doses hypodermically may control the convulsive movements, but it has no effect on the condition of the kidneys. If there is suppression of urine, if the quantity is diminished to a considerable extent, even if there are no convulsive movements, the hot pack and the injection of the normal salt solution should be immediately resorted to. It is better to ward off the convulsions by the method of treatment just described than to wait until the more pronounced symptoms of uræmia are in evidence.

The after treatment of nephritis consists of a careful regulation of the diet and the administration of iron. Eisenzucker and Basham's mixtures are satisfactory preparations. Rheumatic fever occurring in the course of scarlet fever must be treated by the usual remedies, but a differentiation must be made between this condition and arthritis due to streptococcus infection. In this latter condition gaultherium applied to the painful parts is of benefit.

There is no special treatment for the heart and lung complications. An early operation in cases of empyema is advisable.

Serumtherapy.—The treatment of scarlet fever by antistreptococcic serum has not, so far, been productive of much good. In a marked septic case of the disease, with a profuse nasal discharge, cultures from which show the presence of streptococci, the antistreptococcic serum may be used as a last resort. In the experience of the writer the serum has not seemed to do any good, although there is no evidence that it has done any harm. It is, therefore, advisable to administer it.

Until it can be absolutely settled that streptococci are the cause of the disease and until there is a definite way of differentiating the varieties of streptococci, the subject of serumtherapy must remain in abeyance.

Escherich and Moser, in the Annakinderspital at Vienna, since 1902 have had remarkable results in the serum treatment of scarlet fever. The dose of the serum is quite large, being 200 cc., but no injurious results have been noticed. Shaw says that the mortality average in this hospital was 14.5 per cent. for four years before the serum treatment was adopted, and that since its use the average mortality rate for four years was 8 per cent. He also says that for the same period in other scarlet fever hospitals in Vienna the mortality when the serum was not used averaged 13.1 per cent. According to Shaw, Moser employs the following method in the preparation of the serum:

"The horses receive injections of bouillon culture of streptococci direct from the child. Up to the present time he has isolated nearly thirty different types of streptococci, and as he injects them all his serum is a true polyvalent one. He has also shown that these streptococci differ from those found in the other streptococcic diseases of man, such as erysipelas, etc. When sufficiently potent, the serum, in a dilution of 1 to 250,000 should agglutinate the streptococci." At the present time this serum cannot be obtained in this country, as it is prepared only at the Vienna Serum Institute; therefore we cannot state, from experience, anything regarding its efficacy.

The injection of the serum of the blood of convalescent scarlet fever patients has been tried in the treatment of severe attacks. A sufficient number of cases are not on record to justify any opinion regarding the efficacy of this method. On general principles, however, it is extremely doubtful if any benefit can be derived from this treatment.

CHAPTER XIII.

MEASLES.—RUBELLA.—THE FOURTH DISEASE.—ERYTHEMA INFECTIOSUM.

By JOHN RUHRÄH, M.D.

MEASLES.

Synonyms.—Latin, morbilli; German, Masern; French, rougeole; Italian, rosolia; Spanish, sarampion.

Definition.—Measles is a specific infectious disease characterized by extreme contagiousness, fever, catarrhal symptoms, both prodromal and during the height of the disease, a characteristic early eruption in the mouth —Koplik spots—and later by a characteristic enanthem and exanthem and a branny desquamation during convalescence.

Historical.—Measles is mentioned by the older writers, notably by Rhazes, but until the time of Sydenham it was confounded both with scarlet fever and smallpox. Sydenham gave a concise, accurate description, whilst Borsieri, Willan, and others, have given excellent accounts of the disease. The article by Rilliet and Barthez and by Barthez and Sannée, in the last edition of their work, is one of the most instructive. Much of our knowledge is derived from the studies of Panum, who had unusual facilities for observing measles in a community where the disease had not been seen for sixty-five years. This was in the Faroe Islands where, from 1781 to 1846, there had been no measles. In the latter year the disease was introduced from Copenhagen and over 6,000 of the 7,782 inhabitants were stricken. In 1775 it was introduced into the Sandwich Islands and in four months 40,000 of the population of 150,000 died. Pandemics have prevailed in Europe several times, notably in 1834–36, when all northern and middle Europe was affected; and 1842–43 when the disease swept over Russia, Germany, Switzerland, France, and Holland.

Etiology.—At present measles is the most widely spread infectious disease. It is found over the entire world, uninfluenced by climate or weather, except that it is slightly more prevalent in cold weather, which is probably due to people being more crowded together and so giving greater opportunity for infection. The disease is always present in the larger cities, but from time to time epidemics of more or less virulence occur. These are the result of increased virulence of the disease or lessened resistance of the inhabitants, or in some instances of a new set of children having grown up. Now and then a pandemic sweeps over the country. Susceptibility is very great and few are naturally immune. The susceptibility seems to vary from time to time, as individuals may be exposed in one or more epidemics and not take the disease, and then be infected by a subsequent exposure. Few people escape infection permanently. This is well illustrated in three epidemics in the Faroe Islands.

HOFF'S TABLE SHOWING THE EXTREME SUSCEPTIBILTY TO MEASLES. FROM JURGENSEN.

	Number of inhabitants.	Attacked by measles.			Number unaffected.	Those remaining unaffected lived—	
		Epidemic of 1846.	In 1862 or at some other time.	Epidemic of 1875.		In the same house with measles patients.	In house where no measles patients lived.
Thorshavn	930	417	1	506	6	1	5 *a*
Vestmanhavn	315	111	22	139	43	..	..
Kollefjord	223	92	..	120	11	1	10 *b*
Sandwaag	166	35	2	117	12	5	7 *a*
Total	1634	655	25	882	72	..	..

a—In 3 separate houses.
b—In 5 separate houses.

Measles is transmitted by direct contact in nearly every instance. It is probable that the disease may be transmitted by a third person; or by fomites, especially if the time elapsing is not very great, but it is rare for it to be contracted from apartments previously occupied by measles patients. There are numerous instances where families with susceptible children have moved into rooms in which measles patients had been living and there was no infection. If two weeks have elapsed it may be regarded as safe even if the rooms have not been disinfected.

The disease apparently can be carried a short distance through the air. It is well known how difficult it is to isolate measles patients unless a separate open air space intervenes. Instances have been reported where a child has taken measles from a patient on the other side of the ward, with no apparent means of the disease having been transmitted otherwise than through the air. The exposure has been as short as half an hour. In Grancher's wards in Paris, where special studies have been made to determine the transmissibility and the possibilities of preventing its spread, it was found that the infection of measles could be reduced two-thirds, but could not be prevented altogether. It would seem that the contagion varies in virulence, some epidemics being very widespread and others more or less limited, under essentially the same conditions.

The disease is most frequently transmitted through schools. A child in the preëruptive stage can transmit the disease to an enormous number of others, which explains the outbreak of a large number of cases on nearly the same day. Children's parties are another frequent source of infection. A child admitted to a children's hospital or orphan asylum may infect nearly every child in it during the one or more days of the preëruptive stage.

The disease may be transmitted from the time of the first catarrhal symptoms and possibly before, until after desquamation. The infectiousness is very marked early, probably greatest about the time the eruption is coming out and from then until it reaches its height. When the eruption begins to fade the danger of transmission diminishes, and during the stage of desqua-

mation is but slight. Some doubt the possibility of transmission during desquamation and this is a point which cannot be regarded as definitely determined. Until it is, the safer course is to regard the disease as transmissible at this stage. Sporadic cases are occasionally seen in places where the remainder of the inhabitants are immune or live in isolated houses.

Immunity.—Natural immunity is not common, nearly everyone being susceptible to the disease. Nursing infants, especially under five months of age, enjoy a more or less perfect immunity and though closely associated with measles do not often contract it. Instances have been reported where the infant sucked the breast of a woman with measles without infection. After about one year of age and from that upward, the susceptibility is great; and the non-susceptibility of older individuals is to be explained largely by the immunity which they have acquired through having had the disease. The immunity caused by measles is complete and lasting, second attacks being very rare. Panum in his large experience did not report a single instance, and Barthez and Sannée report but three. Maiselis collected a hundred and six undoubted cases, of which three were supposed to have had three attacks. The writer has seen one instance of a child having two attacks five years apart.

Congenital measles has been reported a number of times. "A pregnant woman who contracts measles may communicate the disease to her unborn child." The child may be born with the rash in the same stage as that of the mother, or in the catarrhal stage and the rash may come out later. A. Ballantyne has collected 20 cases of congenital measles. He suggested that infection was simultaneous, as the eruptions in both mother and child corresponded. Gibson has reported an interesting case of antenatal measles. The child was the third and the labor normal. At birth there were red spots on the buttocks and the next day there was a typical measles eruption. The two other children contracted measles eight months later and at that time the third child was unaffected. The mother had measles when a child.

Inoculation Experiments.—Measles has never been transmitted to animals; even Grünbaum's experiments with monkeys and a chimpanzee apparently yielded negative results. A large number of reports have been made of human inoculation with nasal mucus, blood, scrapings of skin, and tissue juices, but for the most part, whilst in the main successful, natural infection has not been excluded. Hektoen has apparently fulfilled the requirements by excluding infection by ordinary means. Under strict aseptic precautions he drew blood from the veins of a measles patient and with this inoculated flasks of ascites broth. This mixture was kept for twenty-four hours at 37° C. and at the end of this time the fluid was apparently sterile. Four cubic centimeters of the mixture (50 cc. of ascites broth and 3 cc. of blood) were injected into a young man. On the thirteenth day there was a temperature of 103° F., and on the following day the eruption appeared. There were no catarrhal symptoms in this patient. In a second case symptoms began on the eleventh day and the eruption appeared on the fourteenth.

Pathology.—Measles toxæmia rarely causes death, and the fatal cases are always complicated with other lesions, the most frequent being pneumonia, colitis, and nephritis. Some authorities, notably Henoch, state that in every fatal case of measles patches of pneumonia can be demonstrated.

The changes in the mucous membranes and the skin are the most striking features of the disease. Unna describes the changes in the skin as a spastic

condition of the bloodvessels. The ducts of the sweat glands are œdematous and the lymphatics distended, but there is no cellular exudate. There is no mitosis during the inflammatory stage, but karyokinesis may be demonstrated during desquamation. Catrin has described the changes as an infiltration of the skin with a sort of colloid material which eventually leads to coagulation and subsequent desquamation of the dead epidermis. Others describe somewhat similar changes, and include cellular infiltration as well. The changes in the mucous membranes are of the nature of a catarrhal inflammation. Every mucous membrane in the body may be affected, but the most marked changes are in the conjunctivæ, nose, mouth, throat, larynx, trachea, bronchi and lungs. Focal necroses have been described in the liver.

Incubation.—This is variously stated as one counts from the appearance of symptoms or to the appearance of the eruption. Symptoms appear from nine to eleven days, and the rash quite uniformly on the thirteenth or fourteenth day after infection.

The Prodromal Eruptions.—The prodromal rashes of measles have received but scant attention. Thursfield has called attention to a scarlatiniform and sometimes to a papular rash appearing twenty-four hours before the regular eruption. J. D. Rolleston has made a careful study of the subject and found prodromal rashes in 30 cases, or 42.8 per cent., of all observed. The day of the appearance of the rash was 22 on the first, 3 on the second, 4 on the third, 9 on the fourth, 3 on the fifth, 2 on the sixth, and 1 on the eighth day. In 18 cases the rash appeared on the same day as the catarrhal symptoms. The character of the prodromal rash varies. In 10 cases it was a blotchy erythema, in 9 an urticaria, in 9 scarlatiniform, and in 1 a circinate erythema. The eruption was on the trunk in 28 cases, behind the ears in 15, on the limbs in 14, on the face in 4, and on the neck in 2. There was no evidence of irritation, and in all cases the rash was transient.

Symptoms and Course.—After infection there is an incubation period, generally of ten days, in which there are no very apparent changes. The general health is good and as a rule the child does not complain. A loss of weight begins on the fourth or fifth day after infection according to Meunier. There is also a leukocytosis during the incubation. Slight changes of temperature have been observed but are not constant, and there is no reason to believe that they are of necessity a manifestation of the incubation period. Prodromal rashes are neither constant nor characteristic. Malaise, depression of spirits, and drowsiness, have been noted, but these are inconstant and frequently absent. There is nothing, unless it be a loss of weight and a leukocytosis together, on which one could base even a tentative diagnosis of measles. Of course the history of exposure is of value, but it is often unobtainable.

The symptoms may be divided into three stages: the period of the invasion or catarrhal stage, the period of the eruption, and the period of desquamation.

The period of invasion is ushered in by numerous symptoms, which make a tentative diagnosis probable if a previous exposure suggests measles. About the ninth or tenth day after infection the child becomes listless and drowsy. The drowsiness is such a constant feature as to be regarded by some of the laity as almost pathognomonic. The child is languid, does not wish to play and seems depressed. The appetite is poor or lost, and if the child is old enough to describe the symptoms there is complaint of headache,

chilly sensations, and of feeling tired. There may be slight or high fever. On this or the following day marked catarrhal symptoms appear, the conjunctivæ become injected and slightly reddened, there is coryza with sneezing, the throat is slightly reddened, and there is some cough and often hoarseness. These symptoms increase in intensity, and after three or four days the child has inflamed and swollen conjunctivæ with usually more or less lachrymation and some photophobia. The coryza is intense and there is a severe bronchitis and frequently hoarseness. In some cases these symptoms are mild and there is but little fever, whilst in the severest cases the child is extremely miserable and may be completely prostrated. The eruption is first visible in the mouth and then appears on the face about the margin of the hair and spreads as described above. The temperature may drop after the rash makes its appearance or continue for a day or two longer. The symptoms are usually most intense about the height of the rash; as it fades they lessen, and by the time the rash has faded the child feels fairly comfortable.

The lymph nodes all over the body become enlarged, particularly the postcervical and postauricular ones; but this may in some cases be wanting. They rarely attain the size seen in rubella. The spleen is usually slightly enlarged. Heim has called attention to the odor of measles, which he likens to that of freshly plucked goose-feathers. It is very perceptible in a ward full of measles patients, but is too faint to be detected by the average nose in isolated cases. It is a sweetish, heavy odor suggestive of sickness.

Koplik Spots.—The most valuable recent contribution to measles has been made by Koplik. The rash had been noted in the mouth and excellent descriptions of the spots given by Filatow, Flindt, Reubold, and Bohn, but they apparently did not appreciate their significance. Koplik's[1] original description cannot be improved upon: "If we look in the mouth at this period (invasion), we see a redness of the fauces; perhaps, not in all cases, a few spots on the soft palate. On the buccal membrane and inside of the lips, we invariably see a distinct eruption which consists of small, irregular spots, of a bright red color. In the centre of each spot there is noted, in strong daylight, a minute bluish-white speck. These red spots, with accompanying speck of bluish-white color, are absolutely pathognomonic of beginning measles, and when seen can be relied upon as a forerunner of this eruption. No one has, to my knowledge, called attention to the pathognomonic nature of these small bluish-white specks and their background of red, irregularly shaped spots. They cannot be mistaken for sprue, because they are not as large nor as white as sprue spots. These specks of bluish-white surrounded by a red area are seen on the buccal mucous membrane and on the inside of the lips, not on the soft palate. Sometimes only a few red spots with this central bluish-white point may exist—six or more; and in marked cases they may cover the whole inside of the buccal mucous membrane. If these bluish-white specks on a red spotted background are at the height of their development, they never become opaque, as sprue, and in this respect, when once seen, are diagnostic, nor do they ever coalesce to become plaque-like in form. They retain the punctate character."

"The eruption just described is of greatest value at the very outset of the disease. As the skin eruption begins to appear and spreads, the eruption on

[1] *Archives of Pediatrics*, 1896, vol. xiii., No. 12, pp. 918 to 920.

the mucous membrane becomes diffuse and the characters of a discrete eruption disappear and lose themselves in an intense general redness. When the skin eruption is at the efflorescence, the eruption on the buccal membrane has lost the character of a discrete spotting and has become a diffuse red background with innumerable bluish-white specks scattered on its surface. The mucous membrane returns to the normal appearance long before the eruption on the skin has disappeared."

In forty cases in which care was taken to look for Koplik spots they were found in 38, or 95 per cent. The spots were noted at the very beginning of the eruption in 13 cases, twelve hours before the eruption in 4 cases, 1 day in 9 cases, 2 days in 5 cases, 3 days in 6 cases, and 4 days in 1 case. As a general rule the spots can be seen in 95 per cent. of the cases of measles, and usually one to two days before the eruption appears on the skin. If care is used they may sometimes be seen much earlier. These spots cannot be seen by ordinary artificial light and are difficult to see except in strong daylight. Of their diagnostic value there can be no question, and practically all observers are agreed that they are pathognomonic of measles. They are not seen in German measles nor in other diseases. O. Müller is one of the few writers who does not place much value on the spots. He claims to have found them in 50 per cent. of his German measles cases. Koplik spots when once seen are easily recognized. They should not be confused with thrush or aphthous ulcerations, nor should the opening of Steno's duct be mistaken for one. They are of great value in the early diagnosis with a view to preventing infection. Prompt isolation on their discovery may prevent many cases.

Flindt has given the best description of the eruption in the mouth, which has been quoted by Jürgensen, from whom the following is condensed: On the first day of the fever there is a slight diffuse redness of the mucous membrane. On the second day there is considerable redness and injection of the pillars of the fauces and of the tonsils. Toward evening there may be slight swelling of the tonsils. There is also an eruption of round, somewhat irregular light-red spots just above the surface, varying in size from a pin-head to a lentil, partly isolated, partly in irregular coalescent groups. Tiny whitish, shiny raised points can be both seen and felt. These are also seen in the conjunctiva. On the third day the mucous membrane of the mouth is normal in color except for the previously described eruption, which covers all but the anterior third of the hard palate and is also seen in the cheeks between the upper and lower molars. The spots on the conjunctiva are obscured by redness. At this point the eruption appears on the skin. On the fourth day the spots are thicker and coalescent and the eruption on the conjunctiva can no longer be seen. On the fifth day of fever the eruption is more distinct, extends to the inner and even outer surface of the lips, and is seen indistinctly on the gums. On the sixth day the eruption has disappeared and there is a diffuse redness of the palate and cheeks. The rash in my experience often persists much longer than the sixth day of fever. The course of the eruption in the mouth, as on the skin, varies greatly, and no set description will cover all cases.

The eruption occurs on all the mucous membranes. Gerhard has described it upon the larynx, trachea, and bronchi. It has been noted on the mucous membranes of the intestine, genitalia, and bladder.

The Exanthem.—"The symptoms increase until the fourth day, when (although sometimes a day later) little red spots, just like flea bites, begin to

come out on the forehead and the rest of the face. They increase in size and number, group themselves in clusters, and mark the face with largish red spots of different figures" (Sydenham). The eruption usually appears on the third, fourth or fifth day after the catarrhal symptoms begin. It may come out on the first day after the beginning of symptoms, or be delayed as late as the tenth. In rare atypical cases the rash, it is said, may be absent entirely. Variations in the appearance of the rash are more frequent in young children.

The rash appears first on the temples, the forehead about the edge of the hair, and back of the ears, as small red spots. These are seen a little later or even at the same time scattered over the body, both back and front, and at this time there is often a mottling or marbling of the skin as if the eruption were beginning deep down. There may be at the start irregular crescentic patches. The eruption consists of minute pin-head sized papules, slightly elevated and as a rule easily felt. These are grouped sooner or later in crescentic patches about a centimeter in length. The rash spreads from one part of the body to another, the face being first affected; the eruption can be seen on the scalp and then spreads over the back, wrists, and forearms. At this time the small scattered spots are seen on the legs. The rash spreads rather rapidly downward until the palms of the hands and the soles of the feet are affected. The flexor and extensor surfaces are affected about equally. The rash in some places is so thickly set that it forms continuous red patches, as is frequent on the face and upper part of the chest. The extent of the eruption varies considerably and some have but a few blotches whilst others may have the entire body almost uniformly covered. The skin is really never affected in its entirety, and, even where the rash is most marked, normal skin may be made out by pressure or by stretching it.

The earlier spots are of a rose-red color and rather bright. The eruption later becomes somewhat the color of a purple raspberry and has a characteristic tint, becoming somewhat darker as time goes on until it is nearly a port-wine color or the shade of a purple birth-mark. After several days it fades rather quickly, leaving purplish brown spots which in a day or two become faint yellowish-brown in color. The slight pigmentation persists from two to three weeks. The eruption fades about in the order it appeared, and may begin to disappear from the face before it has fully developed on the feet and ankles.

The small papules are sometimes surmounted by a tiny vesicle, whilst in others there is merely a small elevated point. In some cases the papules are larger and have a distinct shotty feel like smallpox, rendering the diagnosis difficult. Small petechiæ are common in some cases, particularly about the wrists and ankles. They are seen in about 5 per cent., and are easily produced by slight bruising or pinching a fold of skin between the fingers. This should not be mistaken for a hemorrhagic rash. A distinctly hemorrhagic rash, where there is hemorrhage into or about the great majority of the spots, is not very common. It occurs in the severest form of the disease and is spoken of as "black measles." Coming on early, as the eruption appears, it is nearly always the sign of a fatal issue. When it appears later the prognosis is not so hopeless, although always grave.

There are many curious anomalies; thus the eruption may remain incompletely developed and give the appearance of being deep in the skin. It may run an extremely rapid course or be unduly prolonged. It may fade in

an irregular manner, remaining longer on the face or elsewhere than would be expected. There may be free perspiration in many cases whilst in others there is a considerable itching, the skin being broken and ecchymotic spots caused by the scratching.

The rash varies in appearance from many causes. It is made more intense by the patient being in a warm room or a warm bed, and it is sometimes the custom to increase the amount of bedclothing and make the room unduly warm in order to "bring out the measles." If the rash is not definite it may often be brought out by a warm bath, as is sometimes done for diagnostic purposes. Exposure to cold will contract the skin arterioles and cause the rash to fade, as is frequently seen in dispensary practice when a child is brought from a warm room to the dispensary on a winter day. The rash may be almost entirely obliterated, especially early in the disease. Another cause of the rash fading is heart failure. This rarely happens from the measles toxin alone, but may frequently be seen with severe complications. The laity say that the "measles has struck in," and it is regarded as a very bad omen. When the fading is due to heart failure this is true, and stimulation is indicated.

Sometimes a pemphigoid eruption is seen during the course or later and this may occur about the fifth or sixth day with a rise of temperature and marked constitutional symptoms. There are large flat vesicles, often filled with thin pus and sometimes bloody serum. Slow recovery may take place, or the patches become gangrenous and death follow. There may at the same time be other septic complications such as pericarditis, endocarditis, pleurisy, and arthritis. Sometimes an occasional bulla is seen, without the grave prognosis of the pemphigoid form. Gangrene of the skin or of the genitals may follow measles. Ecthyma, furunculosis and impetigo contagiosa are often mentioned in connection with the rash, but belong properly to complications. Machold has described a curious post-measles eruption. Fourteen days after the attack the entire body was covered with a bluish, macular eruption lasting three days, which was followed by slight desquamation. There was no rise of temperature, no constitutional disturbance, and no drugs had been given.

Desquamation follows nearly every case of measles but may be so slight as to escape detection. If the skin is thoroughly cleansed daily and oil or an ointment applied, the eruption is scarcely noticeable. The usual desquamation consists of small bran-like scales, and lasts from one to two weeks or occasionally longer.

Measles without an exanthem is an anomaly which on good authority is said to be occasionally met with. Embden claims to have seen 20 in an epidemic of 461 cases. Thomas and Rilliet also claim to have seen it. The diagnosis is allowable only in an individual who has never had measles and who, during an epidemic, with ample opportunity for exposure, has a diseased condition resembling measles in all particulars except the failure to have the skin rash. Some may be explained by measles with a rash of short duration, an anomaly much more frequent than the absence of rash entirely.

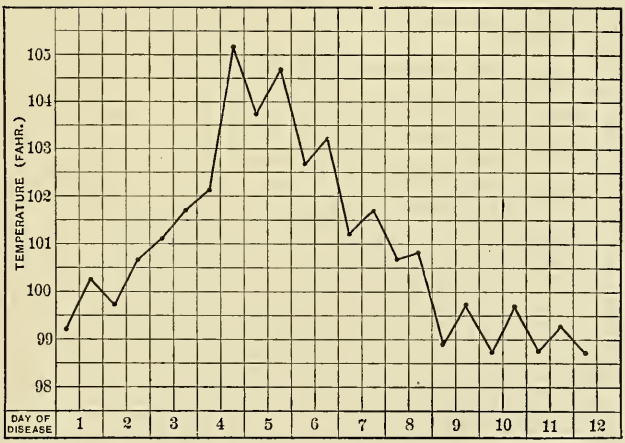
Anomalous Cases.—These are frequent; thus the disease may be slight, with few or no symptoms, little fever and a light eruption, or the rash may be quite pronounced, or any of the more noticeable symptoms may be absent. Thus one patient may be seen without any conjunctivitis or photophobia, and another with little or no bronchitis. On the other hand any or all

symptoms may be very intense either at the outset or at the beginning of the eruption. There may be extreme headache with photophobia suggesting meningitis, or convulsions at the onset, or intense drowsiness amounting almost to coma. Epistaxis and other hemorrhages may occur especially on the third or fourth day. Catarrhal symptoms of a most intense grade may be present and bronchitis so severe as to cause alarm. There may be croupy attacks or intense hoarseness with symptoms like pharyngeal diphtheria. In some instances false membranes may form in the larynx, due to streptococci or staphylocci, which may cause obstructive symptoms so severe as to require intubation. Neurotic children and those who have had whooping-cough may have an intense spasmodic cough difficult to control. Occasionally there may be joint pains and even arthritis with effusion.

Malignant Measles.—The disease may at times be of a particularly malignant type. This may be manifest from the onset or become so at the stage of eruption. The malignancy in some instances is manifested by hyperpyrexia. The child may have a continuously high temperature which suddenly goes up to 107°–109° F., and death ensues with no other symptom of note. Another form is the hemorrhagic or "black" measles, in which, usually at the onset of the eruption, there are hemorrhages into the skin as well as epistaxis and other hemorrhages. There may be high fever with intense prostration, and death may be caused by hemorrhage or the intensity of the toxæmia. In other malignant cases there are severe symptoms, headache, vomiting, diarrhœa, high fever, a weak rapid pulse, often hemorrhage and intense nervous features, convulsions or coma, and death.

Temperature.—This does not follow any very definite course although usually there is a great similarity. The temperature charts of nearly a

FIG. 41.

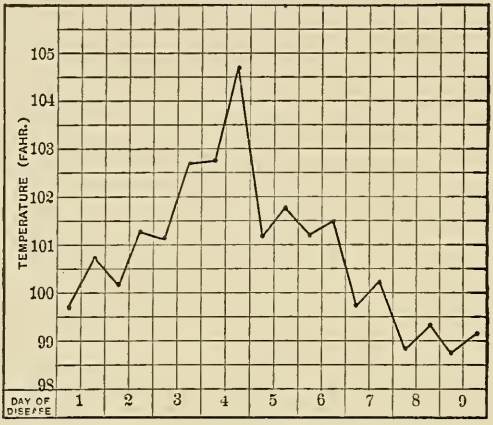


Measles temperature chart.—Case of moderate severity, showing rather abrupt rise at beginning of eruption. Personal observation.

hundred cases show the following facts: As a rule there is no fever during the incubation period. With the onset of the catarrhal symptoms the temperature begins to rise and reaches 100° or 101° F. in the evening. The following morning it falls as a rule, although it may remain the same or even go higher.

The temperature rises every evening to remit slightly on the following morning until the third or fourth day, when 104° or 105° F. is reached. With the appearance of the rash the temperature falls slightly and during the next few

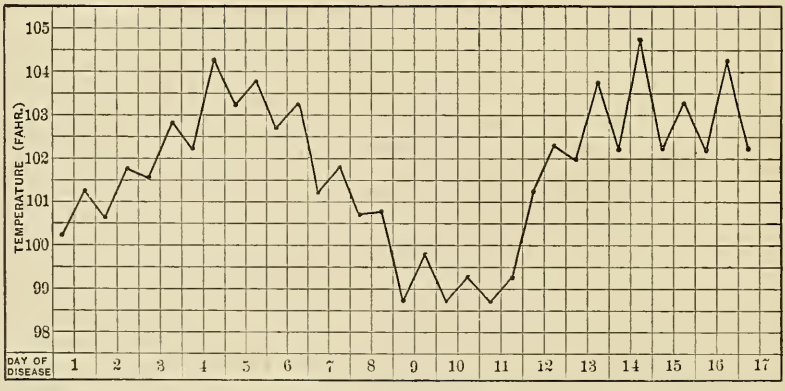
FIG. 42.



Measles temperature chart.—Showing sudden fall at the appearance of the eruption. Personal observation.

days is lower and lower each morning with a slight increase in the evening until normal is reached. This in uncomplicated cases seems to be the most general course. It not infrequently happens that, at the beginning of the symptoms, there is a sharp rise to 103° or 104° F. and then after several hours a fall to normal, then following the regular rise just described. In exceptional cases

FIG. 43.



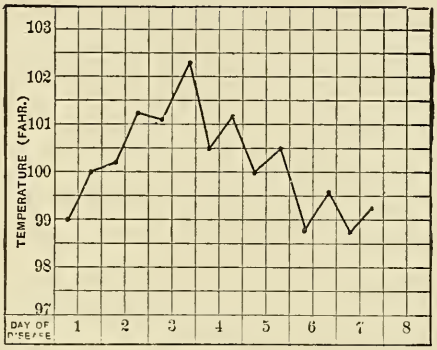
Measles temperature chart.—Showing a complicating pneumonia coming on after the temperature had fallen to normal. Such a temperature can always mean a complication.

it may rise suddenly at the invasion and remain high with slight morning remissions until the eruption appears. Another common occurrence is a sudden drop in the temperature with the appearance of the rash. The temperature may fall to normal, below it, or to 100° F. or thereabouts. In some

there is no subsequent rise of any importance; in others the temperature may rise to 102° or 103° F. and then fall during the next two or three days.

Any sudden rise in temperature a day or two after the eruption is out may be regarded as an indication of some complication. If the temperature

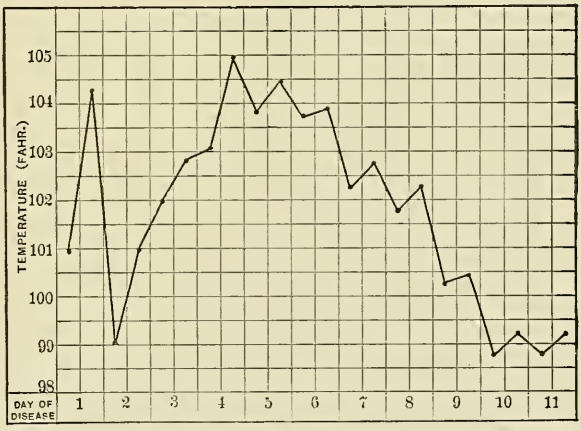
FIG. 44.



Measles temperature chart.—Mild case. Personal observation.

remains high for more than a day or two after the eruption has made its appearance it indicates the same thing. In the majority the complication affects the respiratory tract, and the lungs should be examined with especial care. Otitis media is another and a frequently overlooked cause of high temperature.

FIG. 45.



Measles temperature chart.—Showing initial rise and fall. Personal observation.

Blood.—Tileston has made an interesting study of the blood in measles. There is a leukocytosis beginning early in the period of incubation, reaching its maximum six days before the appearance of the eruption and lasting into the first part of the stage of invasion. During the latter part of the stage of invasion and the beginning of the eruptive stage the leukocytes fall to normal or there may be leukopenia. During this period a leukocytosis means some

complication, although complications may exist without any leukocytosis. Differential counts showed that the polynuclear neutrophiles are increased during incubation, invasion, and eruption, fall to below normal at defervescence and reach normal in convalescence. The lymphocytes are decreased at first but increased after the crisis. The large mononuclears and transitionals are normal at first but increased in the later stages. Eosinophiles are decreased during the eruption but increased later. Myelocytes are present in small numbers during the eruption. The normal leukocyte count is generally reached at the fifth day of the eruption.

The study of the blood has some value in diagnosis between scarlet fever or measles. In scarlet fever there is a leukocytosis. As regards prognosis from the blood examination it is stated that if more than half the leukocytes are absent the prognosis is bad. If there is but a slight diminution the outlook is good. The blood findings may be so altered by complications as to be of little value either in diagnosis or prognosis, a point which should be borne constantly in mind.

The Urine.—Albuminuria is usually present during the febrile period, but nephritis is rare. The diazo reaction is found in about 80 per cent. of the cases. It comes on with the eruption and attains its maximum intensity with the height of the fever. It may be present half a day before the exanthem appears, and disappear with the fever, but in some instances persists as long as five or six days after the temperature is normal.

Complications.—These are frequent and very important. It is sometimes difficult to draw the line between symptoms and complications, but in general this offers no real difficulty. Almost every case of measles presents a complication of some kind. Barthez and Sannée, in 1,521 cases found 1,044 with complications.

Eye Complications.—Injection of the conjunctiva and usually a distinct conjunctivitis, which occasions a certain amount of photophobia, and often blepharospasm, always occur. If the child is kept in a darkened room and some mild antiseptic eye wash applied frequently there is generally no further trouble. Schottelius studied the bacteria present, and found that the staphylococcus aureus was the most frequent organism. The inflammation may extend to the lachrymal gland. Hordeolum (sty) may be present and blepharitis is common. The cornea is not infrequently inflamed. There is usually merely a superficial keratitis, but a diffuse keratitis or even ulceration may occur. There may be weakness of accommodation after measles, and paralysis or spasm of the ocular muscles has been reported. Amblyopia is rare and in some cases it has been followed by optic atrophy.

Ear Complications.—An acute catarrh of the middle ear is not infrequent from extension of the inflammation in the nasopharynx along the Eustachian tube. It may cause earache, slight deafness, or tinnitus. Occasionally the inflammation becomes purulent and the ear-drum ruptures. Mastoid abscess rarely complicates the middle-ear disease.

Gastro-intestinal Complications.—Stomatitis is present in every case. Ordinarily there is merely the enanthem with more or less catarrhal stomatitis, but the other forms occur. Aphthous stomatitis is not as common as the ulcerative form. Thrush may be met with in young infants and those poorly cared for. The ulcerative form of stomatitis may be of a most severe type and prove serious; the teeth may be lost or necrosis of the jaw follow. A curious membranous stomatitis may follow measles, frequently in con-

nection with ulcerative stomatitis. A thick yellowish membrane may cover part of the cheeks and gums, and be attended with considerable ulceration. This occurs in children weakened from other complications, and usually terminates fatally. Gangrenous stomatitis is occasionally seen after measles, and is one of the most horrible complications. The destruction of tissue is painless and rapid, and there is a characteristic fœtid odor. It is practically always fatal. Glossitis occurs now and then and causes considerable discomfort. Heberden has reported curious cases of constant spitting both day and night, coming on with the eruption and lasting for a day or two.

Vomiting is not more common than in the other febrile diseases of children. Whilst acute gastritis occurs, disease of the intestines is more frequent, diarrhœa often being present, and ileo-colitis is one of the major complications. In the severest form the colon and lower part of the small intestine are affected. The catarrhal and ulcerative forms are most frequent but membranous colitis may be met with. Colitis is always to be regarded as a serious complication and treatment should be prompt and energetic. Hicks has reported a case of general peritonitis following measles in which recovery took place in three months.

Complications of the Respiratory Tract.—These are the most frequent of all. Nearly every patient has coryza which may now and then be purulent. The larynx is frequently inflamed and there is hoarseness, croupy cough, and sometimes loss of voice and symptoms of obstruction. These may be difficult to differentiate from laryngeal diphtheria. Severe laryngeal inflammation is always to be regarded as a dangerous complication and membranous laryngitis is second to pneumonia as a cause of death in measles. The streptococcus is usually present but some are true diphtheria. Caillé has called attention to persistent hoarseness following measles.

Tracheitis, tracheobronchitis and bronchitis are all frequent. The bronchitis may extend into the smaller tubes, a condition described as bronchiolitis or capillary bronchitis by some authors, but one which does not differ clinically from bronchopneumonia. There is severe cough, dyspnœa, and cyanosis, the pulse becomes rapid and weak, and death may ensue. The physical signs are the sinking in of the ribs during inspiration and numerous fine rales heard all over the chest, while coarser rales are not uncommon. Areas of dulness cannot be made out. The breathing is shallow, the diaphragm in consequence is high, and the liver dulness may be mistaken for consolidated lung. The heart dulness is usually enlarged owing to acute dilatation. This form of bronchitis is usually seen about the height of the eruption.

Bronchopneumonia is the most frequent of the more serious complications and is responsible for more deaths than any other cause. Henoch states that some pneumonia is found in every fatal case. The symptoms, course, and physical signs do not differ from ordinary bronchopneumonia, but it should be borne in mind that in measles the temperature cannot be relied on to differentiate a pneumonia and a bronchitis. If there are symptoms of bronchopneumonia, even though not marked, it is safe to assume that it is present. The lungs should be examined in every patient. If the temperature is above the average the presence of pneumonia should be suspected. The child is dull and apathetic as a rule and the respirations are rapid and often irregular. The physical signs are more marked over the back and there are often small areas of consolidation near the spine in both

lower lobes. These are made out by the presence of fine crepitant rales which remain localized in spite of attacks of coughing, while the coarser rales heard throughout the chest are modified after a coughing spell. These areas spread until the patch may be made out by percussion and usually also by loud bronchial breathing. Sometimes the respiration over the affected area may be very much diminished owing to the blocking up of a bronchus with secretion. This frequently disappears after coughing.

There is no regular course for a bronchopneumonia; it may last a week with irregular fever or persist for six weeks, the fever running now high, now low, sometimes subnormal, sometimes above 105° F. Other complications may render the case hopeless or the child may die of toxæmia, heart failure, or, in some cases, from suffocation, being too weak to keep the bronchi clear. The process may stop and go on to recovery at any time. Following bronchopneumonia, especially a persistent attack, there may be bronchiectasis. Chronic interstitial pneumonia is also not infrequent.

Bronchopneumonia is frequent in asylums and hospitals and among the poor, and occurs more often in weak than in robust children. It is more common in overcrowded wards than where there is sufficient air space and ventilation. Exposure to cold in going to the closet or using a chamber is a frequent cause. In cold weather, in an overcrowded ward in an institution for children, nearly every case of measles may be complicated with pneumonia.

Lobar pneumonia is not frequent. Congestion of the lungs is sometimes seen, and these cases are regarded by some as abortive pneumonia. The temperature is high for a day or two, the child is prostrated, somewhat cyanosed, and the respiration rapid. Physical signs show diminished breathing over the congested area, sometimes over both sides of the back, but after one or two days the symptoms disappear.

Empyema is of considerable gravity. There may be pneumonia with pleurisy or the pleura may be involved later. If empyema is suspected the needle should be used and if pus is found it should be evacuated. Gangrene of the lungs may follow empyema and the writer saw four such cases in one epidemic. Gangrene of the lung or abscess of the lung may follow the pneumonia without an empyema and both are nearly always fatal. Pleurisy may be a frequent complication in certain epidemics. Gutteeit reported an epidemic in which hydrothorax was a frequent and a fatal complication.

The peribronchial and mediastinal lymph nodes may become enlarged after an attack of measles with pulmonary complications.

Circulatory Complications.—Involvement of the heart is not common unless other complications are present. Pericarditis is sometimes seen but more frequently escapes notice until the autopsy. Endocarditis is rare, and myocarditis, whilst not infrequently found at autopsy, is probably due to the complication which caused death. Occasionally œdema from heart insufficiency may be noted. Phlebitis with the formation of thrombi is a rare complication, and when it occurs the sinuses of the brain and the kidney are the most liable to be affected.

Polymyositis and polyneuritis have been reported by Jessen, coming on ten days after the eruption and attended with swelling of the muscle and œdema.

Nervous Complications.—These are various and include almost every nervous disease. Convulsions are occasionally seen at the onset, and head-

ache, backache, and neuralgia, are not infrequent. Contractures of the muscles are sometimes seen early and during convalescence. Various forms of paralysis, hemiplegia, paraplegia due to myelitis, and general neuritis, have all been reported but are rare. Alluria has recently published a case of neuritis limited to the peroneal nerve in which there was paralysis which subsequently disappeared. Scheppers has reported a case of aphasia with difficulty in making complicated movements, but after two weeks' recovery slowly took place. Temporary insanity, chorea, and epilepsy, have all been ascribed to measles.

Skin Complications.—These are numerous, urticaria, furunculosis, impetigo contagiosa, and ecthyma, being the most frequent. Erythema nodosum and erysipelas have been reported. Pemphigus is one of the most serious; it may be very extensive and accompanied by severe constitutional symptoms. Many prove fatal, as do those in which the skin becomes gangrenous. Gangrene of the skin may occur alone but is usually an extension of gangrene starting in the cheek or about the vulva. Measles is reported as having sometimes a curative effect upon eczema, particularly of the facial type.

Bone and Joint Complications.—Goldthwait has reported osteomyelitis of the tibia with mild pericarditis ten days after measles, and necrosis of the jaw from ulcerative stomatitis has also been seen. Arthritis may occur as a rare complication, the knee being most frequently affected.

Inflammations of or about the genitalia may be noted, particularly vulvovaginitis. Subcutaneous abscesses may be seen occasionally.

Pregnancy and Measles.—Cerf has studied the effect of measles in pregnancy, and his figures show that it causes abortion in 60 per cent. of the cases. The more advanced the pregnancy the more probable is abortion, and after the seventh month in 80 per cent. there was premature birth. There are no post-partum complications in these cases.

When measles and chickenpox are seen together they both run their accustomed courses. Blochett saw two cases in which, after the eruption of chickenpox had been present for two or three days, the eruption of measles appeared. The chickenpox was so obscured that its presence would not have been suspected had it not been previously seen. Smallpox and measles together may produce a difficult clinical problem. The measles exanthem may be distinguished between the pocks, but if the smallpox is confluent the measles eruption may be indistinguishable on the face. According to Leech when measles and varioloid are seen together each runs its course uninfluenced by the other.

Tuberculosis may be regarded as a complication or a sequel of measles. An attack of measles undoubtedly lowers the resistance, and any infection may, of course, be seen as a complication. Tuberculosis at this time may mean extension from some preëxisting focus, as a tuberculous lymph node, usually bronchial or mediastinal, or it may mean infection from outside.

Diagnosis.—This is usually easy after the rash has appeared although at times it may test the ability of the clinician to decide upon the nature of a morbilliform rash, and cases without eruption are almost always doubtful. To be of the greatest preventive value the diagnosis should be made early, in the preëruptive stage if possible. The early leukocytosis is of value, if a blood count can be made. If measles is suspected, the drowsiness, or the cough, coryza, and conjunctivitis, are sufficient to make a tentative diagnosis.

Koplik spots are of especial value, and the most frequent cause of failure to find them is not their absence, but a lack of knowledge of their appearance, the use of poor or artificial light, and a too hurried examination.

Meunier has called attention to a loss in weight of children during the incubation period, which he regards of value in early diagnosis. On the fifth or sixth day before the appearance of the catarrhal symptoms, there is a loss of weight of about 10 ounces in a child of from one to four years of age. The loss may be as much as 3 ounces daily, and is independent of age or of the severity of the attack.

Scarlet fever is distinguished by the sudden onset with vomiting and high fever, the characteristic rash, the angina, and the strawberry tongue. Rubella is very easily confused with measles, but in epidemics the absence of catarrhal and other symptoms, absence of Koplik spots, the presence of the characteristic enanthem, and especially the polymorphous character of the exanthem, make the diagnosis easy. (See Rubella.)

Smallpox is the most important disease with which measles may be confused. Despite the apparent difference, the two diseases may be strikingly similar, especially about the beginning of the rash. Measles is, perhaps, more often mistaken for smallpox than the reverse. In smallpox there is, usually, an initial chill, vomiting, backache, and fever, and when the eruption appears the fever falls, and the patient feels comparatively well. Measles begins as described above, with catarrhal symptoms, and the fever does not as a rule disappear when the rash makes its appearance. There may be severe symptoms in measles at the onset, and with the appearance of the eruption the temperature may fall, although this is not the rule. Add to these anomalous conditions a measles rash having a distinctly shotty feel and the picture may be almost, if not exactly, the counterpart of smallpox, as the writer has had opportunity to witness. The following points are of value: The measles enanthem is finer, much more abundant, and more in patches, than the eruption of smallpox as seen in the mouth. On the first day or two of smallpox there are small red papules seen best on the palate. Koplik spots, if present, are valuable, even pathognomonic, but in these instances they may be obliterated before the patient is seen. The exanthem of measles is frequently confluent on the face, chest, and back, while smallpox is rarely confluent on the trunk but frequently so on the face, forearms, and wrists. The measles eruption is arranged in crescentic patches, while the smallpox eruption is not. The measles eruption may be seen on the conjunctivæ, whilst smallpox may, but does not always, affect the eye. The history of exposure to one disease or the other is of some value. Should doubt exist it is better to isolate the patient and wait for twenty-four hours, when the diagnosis is usually clear.

The prodromal rashes of smallpox may be morbilliform, and have been mistaken for measles. The absence of Koplik spots and catarrhal symptoms render it plain that the rash is not measles, whatever else it may be.

Typhus fever has the same catarrhal symptoms, but the general symptoms of the disease are more intense. The onset in typhus is sudden; the eruption becomes hemorrhagic after the first two or three days, and has not a morbilliform character, but consists rather of spots and blotches. The extreme rarity of typhus fever, nowadays, is a point in favor of any given case being measles. It should be remembered, however, that some recently observed cases of typhus have been first called hemorrhagic measles.

Influenza or grippe is sometimes mistaken for measles at the onset, as the symptoms may be very much alike. The absence of Koplik spots is of value. Barthez and Sannée regard vomiting at the outset as an indication of measles rather than of influenza Septic infections with rashes are much more liable to be mistaken for scarlet fever than measles. The absence of Koplik spots and of the eruption in the mouth generally suffice to distinguish them from measles. The catarrhal symptoms are usually wanting.

Syphilitic rashes may occasionally be morbilliform, and, if there is fever at the same time, may be mistaken for measles The presence of other manifestations, and the longer duration of the rash, are the most distinguishing features. The enanthem in these cases is of particular diagnostic value.

Serum rashes are usually scarlatiniform or urticarial, but now and then may resemble measles. The history of the use of serum, and the absence of the characteristic enanthem and prodromes, make the diagnosis easy. Drug rashes are extremely liable to be confused with measles, as there are many drugs which may cause a morbilliform rash. The history of taking the drug, the absence of symptoms, of catarrhal conditions, and of fever, and especially of Koplik spots or other enanthem, will in nearly every case make the diagnosis plain. When the disease for which the drug was taken presents catarrhal symptoms and fever at the time of the appearance of the rash the diagnosis may be difficult. Antipyrine is the most frequently used drug which produces a measles-like eruption. The arrangement is liable to be less crescentic than in measles and it does not spread from above downward. Measles has, as a rule, a spreading eruption.

Quinine may also cause an eruption, but as a rule the rash, even when measles-like, is much more blotchy and urticarial in character than measles. Quinine rashes very much like measles have been described, and some of them even had spread from above downward. Copaiba, cubebs, and other balsams, ethereal oils, turpentine, chloral, and other drugs, may cause morbilliform rashes. In one instance the writer saw the rose spots in typhoid fever so numerous as to suggest measles; there was no crescentic arrangement, and no other symptoms of the disease were present.

Prognosis.—The prognosis in any given case must be guarded; measles is usually regarded by the laity as a mild disease, but when one considers that the United States census for 1900 showed 12,866 deaths, the error of this is very evident. Sydenham said, "They do more to fill Charon's boat than the smallpox itself." The mortality varies greatly in different epidemics, between 3 and 50 or more per cent. In cities the death-rate from measles per 1,000 inhabitants varies from 3.8 to 27.0. The mortality varies greatly with the age and the surroundings. In private practice among the better classes measles is not a very dangerous disease, but among the poorer classes, and in hospitals and asylums, it may prove a veritable scourge. Comby gives the following figures for several of the Paris hospitals:

No. of Years.	Hospital.	No. of Cases.	Deaths.	Percentage
5	Hospice des Enfants-Assistes.....	1575	728	46.22
7	Hopital des Enfants-Malades.....	2585	1048	40.15
5	Hopital Trousseau.....	907	227	25.02

Age is an important factor. From birth to six months of age there are few deaths owing to the comparatively few cases. From six months to two years of age there is a steadily increasing death-rate, which then declines until about the fifth year, after which deaths from measles are comparatively infrequent. The sexes are affected about equally.

Barthez and Sannée give the following figures of age and mortality: 1 year, 62; 2 years, 53.1; 3 years, 34.4; 4 years, 30.3; 5 years, 24.9; 6 years, 17.5; and 7 to 15 years, 9.6 per cent.

After forty the mortality increases with the age, so that in old age it is an extremely fatal malady.

There are more deaths in cold, wintry weather than in summer. This is due partly to the greater number of infections, but more to the greater tendency to pneumonia. The mortality is greater in cities owing to the lessened resistance of the city child, the overcrowding, and lack of fresh air and ventilation. In countries where the disease is introduced for the first time or after a long lapse of years without any measles, it is particularly fatal. Death is nearly always due to complications, the most frequent fatal ones being bronchopneumonia, bronchitis, laryngeal affections, diarrhœa, ileo-colitis, tuberculosis and noma.

The prognosis is bad if the child is between six months and two years of age, if in poor health or suffering with some other disease, and if the hygiene is poor, especially when there is overcrowding and no ventilation. Unfavorable symptoms are high temperature, severe complications of the respiratory or alimentary tracts, and extensive hemorrhagic eruption. Heart failure with fading of the rash is an indication of danger, but this must not be confused with the temporary fading from cold. Rhazes wrote, "When you see the measles of a violet or greenish color suddenly sink into the interior of the body, you may be sure that swooning will come on, and that the patient will die."

Prophylaxis.—Nearly every one has measles some time, and many of the laity take no pains to guard their children from infection. As the mortality decreases after two years of age, and is comparatively slight after five years of age, every effort should be made to put off infection until after the fifth year. Notification of measles is compulsory in most places where there are well-organized health departments. As Panum states, "Quarantine is beyond doubt the best means of preventing the spread of measles." Susceptible children, and, indeed, all visitors, should be prevented from entering houses where there are cases of measles. When this cannot be done among the very poor, the patient should be removed to the municipal hospital.

Children with suspicious symptoms should not be allowed to attend school. Any child with suffused eyes, cough, and sore throat, should be sent home to await developments. Children who have had measles should not be allowed to return to school until all danger is passed. All schools, public and private, should be closed during severe epidemics. Children's parties at similar times should be prohibited. Newman sums up the matter of prophylaxis when he stated that the prevention and control of measles is, like that of whooping-cough or tuberculosis, largely in the hands of the public themselves.

Isolation.—In hospitals and institutions for children every suspicious patient should be isolated. Large hospitals for children would do well to

have a quarantine ward or wards in which children who have not had measles could be isolated from the remainder of the inmates until two weeks have passed, as in nearly every instance epidemics in hospitals are started by the admission of a child in the incubation period. This measure would do much to prevent hospital epidemics, a matter well worthy of consideration on account of their frightful mortality. Hospitals in which there are measles patients should not receive susceptible children. The isolation room or ward should be in a detached building allowing a free air space all around it. Where this is not practicable the room should be as far removed as possible and be strictly quarantined from the remainder of the building.

Isolation in small hospitals and in private houses, unless carried out in this manner, is liable to prove futile. Isolation in a small room off the end of a ward may be better than no isolation at all, but certainly where children are concerned is not very useful. The greater difficulty in isolation consists in the fact that it can rarely be done sufficiently early. The disease may be transmitted before its presence is ordinarily suspected and the children with whom the patient has come in contact are infected before the disease has been diagnosed. This is particularly true in private families, where the question of isolation is an open one. If the susceptible children can be sent away as soon as the disease is discovered that is the best thing to do. Such children should not be sent to homes where there are other susceptible children, as the children so sent are frequently infected and may prove a source of danger to others. If isolation is enforced in the average household it is usually not strict enough to be of service or is started too late.

The question of disinfecting the rooms occupied by the patient is of interest. In hospitals and institutions this should be done, and, also, in private houses when the rooms are to be occupied immediately by susceptible children. If two or three weeks elapse there is no danger from such a house. After measles it is always well to give the apartments a thorough cleaning, and have them well aired for several days. If a patient is isolated all precautions should be taken with the clothing and bedding both of nurse and patient. In private families where strict isolation is not being carried out the linen need not be disinfected, if the laundry work is done in the house.

Treatment.—The child should be placed in a convenient room, and plenty of fresh air is desirable; but ventilation should be accomplished without strong drafts, which may often be done by ventilating through an adjoining room. The temperature should be about 70° F., and kept as equable as possible. There is no advantage in superheated rooms, an idea very prevalent among the laity. As there is usually considerable photophobia the room should be sufficiently darkened to be comfortable to the patient.

It is well to have the skin anointed with some bland ointment, and equal parts of vaseline and lanolin will be found satisfactory. The skin is kept clean by sponging with warm water and castile soap twice daily, after which the ointment is applied. If there be itching, sponging with warm carbolic acid solution (1 per cent.) is useful. There is a rooted objection in most families to using water on measles patients, and when this cannot be overcome or when the child is liable to be chilled by exposure, all attempts at sponging are best abandoned.

The diet should be the same as for any acute fever. Bottle-fed infants should have their food diluted, and older children should be placed upon liquid diet. Milk, soups, and broths, may be allowed and peptonized if desirable. Food should be given at regular intervals, two, three or four hours apart, depending on the amount given at any one time. Plain or carbonated water, lemonade, orangeade, grape juice and water, and similar drinks may be used to allay thirst, and if food is not well taken egg albumin may be given. Alcohol may be used if indicated. After the subsidence of the fever a gradual return to solid food should be made. If gastro-intestinal disorders appear, the usual rules of diet for these should be observed.

Fever.—If this is but moderate, one of the old-fashioned fever mixtures, such as spiritus ætheris nitrosi (℥ij to ℥xx) and liquor ammonii acetatis (℥v to ʒj), in an aromatic syrup may be used. Citrate of potassium (grs. j to v) is also frequently given in syrup of lemon. If the temperature is high and the child restless, a tepid or sponge bath is the best means of controlling it. If there is any objection on the part of the family to the use of water, this may be overcome by advising sponges of half alcohol and water or even more dilute solutions. A cool pack or a cool bath may be used where the other means do not bring the temperature down. A temperature which does not go above 104° or 104.5° F. need not be reduced unless attended by other symptoms. Temperature over 104.5° should always be reduced. An ice-bag to the head is grateful if there is headache. In giving cold baths to measles patients care should be taken to avoid overexposure. If the feet become blue and cold, warmth and friction may be applied to them, and an alcoholic stimulant administered. If the temperature is high and the child feels cold to the touch a warm bath is indicated. Antipyrine is useful in patients with a good strong heart, but need not be given for the fever alone. It is useful in combating nervousness and cough.

Nervousness and Sleeplessness.—These are frequently allayed by bathing or sponging. If these do not suffice, codeia and antipyrine may be given. A child of one year may be given a sixteenth of a grain of codeia with one grain of antipyrine in syrup of orange. This may be repeated, and will be found most useful for controlling nervous irritability and cough. Phenacetine may be given for the same purpose, best in powders.

The Eyes.—The conjunctivitis present in all cases requires the usual treatment of a mild antiseptic eye wash. Ten grains of boric acid with 1 dram of camphor water and 7 drams of distilled water is suitable. If the lids are found adherent in the morning, the edges should be anointed at night and once or twice daily with a salve containing 1 grain of the yellow oxide of mercury to 4 drams of vaseline.

The Nose, Throat, and Mouth.—These should be kept clean by douches, sprays, or gargles. As a rule the nose is best kept clean with a nasal douche which flushes without any pressure, thus avoiding the possibility of forcing the secretions up the Eustachian tube. Dobell's solution is satisfactory for this purpose. The throat is usually best cleansed by using Dobell's solution in an atomizer, but older children may use a gargle. The mouth should be kept clean by a spray or by absorbent cotton wrapped about the finger, and moistened with boric acid solution, Dobell's solution, permanganate of potassium solution, or diluted peroxide of hydrogen.

Laryngeal complications are best treated by inhalations, of which creosote, oil of eucalyptus or compound tincture of benzoin are the most efficient.

A dram (4 gm.) to a pint (500 cc.) of water may be used. This is heated in a croup kettle or any other steam inhaler and the steam inhaled every hour or two, for five or ten minutes at a time. This is also useful in bronchitis and bronchopneumonia. External applications—heat, cold, or counterirritants—may be made over the larynx.

Bronchitis.—Inhalations as advised for laryngeal complications will be found useful. Antipyrine and codeine will be found of service. Heroin hydrochloride may be used if the cough is very irritable. Brown mixture with or without ammonium chloride may be used in older children, and syrup of squills is also useful. The Jackson mixture consisting of equal parts of syrup of squills, syrup of tolu, oil of sweet almond, and mucilage of acacia, given in doses of from one-half to a teaspoonful, is often helpful. In infants and young children drugs which nauseate are best avoided.

Bronchopneumonia.—This is treated as under ordinary circumstances; inhalation, counterirritation, and stimulants, as indicated, are the best forms of medication. The chest should neither be weighed down with plasters or poultices nor should heavy jackets and innumerable undershirts be used. The chest should be allowed full freedom and the air of the room should be kept fresh and gas stoves and unnecessary attendants excluded.

Gastro-intestinal Complications.—Vomiting is one of the most troublesome, and is best treated by withholding all food and giving the stomach a rest. If this does not avail and if the patient is under a year of age or sufficiently tractable the stomach may be washed out. A useful prescription is equal parts of cinnamon water and limewater, of which a teaspoonful may be given fifteen minutes before feeding, and repeated several times if necessary. Effervescing drafts are also useful. Diarrhœa and ileo-colitis are best managed by cleaning the intestinal tract and careful dieting. Bismuth subnitrate is one of the most useful drugs in these conditions.

RUBELLA.

Synonyms.—German measles; French measles; false, hybrid or bastard measles; rubeola sine catarrho; rubeola epidemica; R. morbillosa; R. scarlatinosa; R. nata; rosalia; hybrid scarlet fever; German, Rötheln; French, rubeola, roseole, R. primitive, R. infantile.

Definition.—Rubella is a specific infectious disease occurring in epidemics, characterized by a polymorphous rash which sometimes resembles that of measles and sometimes that of scarlet fever, and sometimes that of both diseases; by little or no constitutional disturbance, and by an almost constant enlargement of the cervical and sometimes other lymph nodes.

Historical.—The first descriptions of the disease are by Hoffman, in 1740, de Bergen, in 1752, and Orlow, in 1758. There have been numerous contributions to the literature, some denying and some affirming the existence of rubella as a separate disease. Henoch doubted its existence, and even to-day some, as Donald Hood, who regards it as a modified measles, question its identity. Strümpell sums up the question as follows: "The existence of the disease is doubted only by those who have never seen it."

Etiology.—Rubella exists as a separate disease, and an attack does not protect against either scarlet fever or measles, nor does an attack of either

scarlet fever or measles protect against rubella. The former is well shown in Thomas's account of the Nitsche family (1872):

	Rubella.	Scarlet Fever.	Measles.
Max.....	Feb. 10.	———	The whole family in July.
George.....	March 26.	Feb. 27.	
Melitta	March 3.	March 23.	

Similar observations have been reported by Rilliet, Emminghaus, Roger, Picot, d'Espine, and others. West is inclined to believe that rubella and measles are closely related. "They resemble each other somewhat as varicella and variola—alike but not the same,—not twin sisters, indeed, but half sisters at any rate."

Rubella occurs in epidemics and is rarely seen sporadically. The sporadic cases are usually part of small family or school epidemics. Epidemics occur in schools, institutions for children, villages, towns, and even entire countries, as in Holland, in 1859, and in Malta.

Rubella may be transmitted by direct contact and by fomites, especially clothing or bedding, but the contagious principle has not yet been discovered. The contagiousness seems to vary in different epidemics. Steiner does not believe it at all contagious. Atkinson and most observers regard it as contagious only to a slight degree, while Edwards, Griffith, and others, regard it as very contagious. In a small epidemic observed by the writer there were 14 cases in a ward containing 22, or 63.6 per cent. The disease was not carried to any other part of the building, although the maids and nurses went about freely and the clothes were sent to the laundry without sterilization. The children with rubella were up and went through the same halls as the other children, but used a separate play-room and were not allowed to come in contact with the children belonging to other dormitories. In this epidemic it appeared as a disease transmitted by direct contact and not by fomites or a third person.

The disease is contagious early, perhaps even before the eruption appears and this lasts as long as the eruption. Comby states that the contagiousness disappears with the eruption.

Sex and Age.—The sexes are affected equally. Scholl has reported a case where the pregnant mother (seven months) transmitted the disease to the unborn child, the disease making its appearance several days after birth. Young infants are as a rule immune. It is most frequently seen in early childhood, whilst other children and adults are less frequently affected. Hatfield states that the liability varies inversely with the age, whilst Ashby regards adults as even more liable if exposed. He cites an epidemic of 27 cases in a hospital in which 8 cases were in nurses and 19 in children. Seitz has reported a case in a woman aged seventy-three years.

Station in Life.—The disease is more frequent among the poor than the well to do, which may be explained by the lessened resistance and the greater danger of exposure.

Immunity.—One attack generally protects and second attacks are very rare.

Incubation Period.—This is ordinarily stated as being from fourteen to twenty-one days. The shortest period is one day (Griffith and Atkinson) and the longest four weeks (Klaatsch).

Symptoms.—Prodromes.—There may be none at all, the rash being the first thing noted; or there may be some indisposition from several hours to two days, and exceptionally as long as four days, before the rash appears. The most common prodromes are headache, backache, loss of appetite, nausea, and sometimes vomiting, slight fever, drowsiness, and, in some, agitation. Convulsions have been reported at the onset and occasional symptoms are redness of the eyes, a little dysphagia, some hoarseness, and occasionally sneezing.

Invasion.—This may be slight or severe. In some the only thing noted is the appearance of the rash, or there may be chilliness, languor, headache, with pain in the back and extremities. There may be more rarely coryza, congestion of the conjunctivæ, slight pharyngitis, hoarseness, cough, nausea, and vomiting. There may be epistaxis, and Priolean has reported an initial hemorrhage from the eyes and ears. Urticaria and other rashes may precede the initial eruption. The stage of invasion may last from several hours to five days; these symptoms show great variations and may disappear before the eruption.

Temperature.—This varies greatly in different epidemics. There may be no fever at all or it may in rare instances reach as high as 104.3° F. When the temperature is high it remains so but a short time. In the average case the fever is slight and lasts from two to four days, ranging from 100° to 102.5° F., with slight evening exacerbations. The highest temperature is seen usually at the beginning of the eruption, and to a certain degree corresponds to it, the most marked rashes being attended with the highest fever. The exacerbations which follow never reach as high a point unless there is a relapse or some complication.

Eruption.—The most characteristic feature is the polymorphism, and in one patient it may resemble scarlet fever rather closely; in the next it may be like measles, whilst in a third it may on one part of the body resemble scarlet fever and on another measles. It may be accompanied by itching or burning, whilst at other times there are no abnormal sensations. In the majority it affects the face and scalp first, then the neck and body, spreading from above downward, involving the arms and lastly the legs and feet. It may spread irregularly and on certain parts of the body be more intense than on others. When more or less continuous pressure is made on the skin, as about the waist or neck band, or on the back or side when the child is in bed, the eruption is more marked. There are patches about the lips in most instances. The eruption may be seen on the palms and soles. In the writer's experience the morbilliform rash is more frequent, and it may be that alone or mixed with other varieties. It is not uncommon to have a measles-like rash over the face and most of the body, whilst over the parts pressed upon, the buttocks and the inner sides of the thighs, it is a scarlatiniform rash. The rash frequently can be seen in the deeper layers, bluish red macules rather crescentic in shape mottling the skin like marble. Later these appear as rose-red spots, made up of numerous small pin-head-sized papules, slightly raised above the surface, and to the touch like shot under the skin. In some the patches are discrete and in others they may run together. The early rash may at a glance suggest flea or other insect bites. In still other cases the little

pin-head-sized papules may be nearly all discrete. The rash fades rather quickly and may be fading on one part of the body while spreading on another. The eruption reaches the greatest intensity usually on the second day and then begins to fade, the entire process lasting from one to two days to a week. The duration of the rash is extremely variable, and it may last but an hour or two or as long as fifteen days. The average duration has been stated as from one to six days, three to four days, and four to five days. The variation in the length of time the eruption lasts is one of the distinctive features of the disease. Cases without any eruption have also been reported.

Following the fading of the rash there may be a light brownish-yellow discoloration of the skin, which disappears completely in from one to three weeks. There may be the separation of fine bran-like scales for several days or no apparent desquamation. Scholl has reported a bran-like eruption lasting for forty days. Purpuric spots, vesicles and petechiæ over the entire body have been mentioned.

The Eruption in the Mouth.—Forcheimer has called attention to the eruption which is seen in the mouth, and this in the writer's experience is a constant feature, being noted at the time of the appearance of the rash on the body. Forcheimer describes it as follows: "It consisted of a macular, distinctly rose-red eruption, upon the velum of the palate and the uvula, extending to, but not on, the hard palate. The spots were arranged irregularly, not crescentically, of the size of large pin-heads, very little elevated above the level of the mucous membrane, and did not seem to produce any reaction upon it." This eruption lasts for twenty-four hours or less, but in some cases it can be seen on two successive days. This eruption in the mouth is unlike that seen in measles and also differs from the scarlet fever angina.

The Blood.—Plantegna has reported findings which resemble those in measles. There is a leukocytosis (polynuclear) during incubation, followed by leucopenia when the eruption appears. After the disappearance of the eruption the blood becomes normal.

Lymph Node Enlargement.—This is a marked feature of German measles. There is a striking enlargement of the posterior cervical lymph nodes much more marked than in measles. This is present in nearly all cases and may also affect the submaxillary, postauricular, and suboccipital nodes. The size varies; they may be small in some or in others as large as a pigeon's egg. The enlargement comes on about the same time as the rash, but may precede it several days. The swelling gradually subsides with or after the disappearance of the rash. The nodes do not suppurate.

Malignant Rubella—Edwards and others have reported fatal cases with vomiting, convulsions, delirium, and high fever. The temperature was high (104° F.) and the heart weak and rapid. The pulse rate in some cases was 150 or over and in some there was heart failure. Pneumonia and diarrhœa were the most common complications.

Complications.—These are rare, but occasionally one or more of the following may be observed: pneumonia, pleurisy, bronchitis, croup, earache or otitis, arthritis, erysipelas, stomatitis, temporary enlargement of the thyroid, convulsions, or delirium. Complications are so rare that they may almost be regarded as coincidences.

Relapses and Recurrences.—Recurrences are very rare as the immunity is apparently perfect and lasting. Relapses are rare but do occur and

DIFFERENTIAL DIAGNOSIS OF RUBELLA, SCARLET FEVER, MEASLES AND ERYTHEMA INFECTIOSUM.

	RUBELLA.	MEASLES.	SCARLET FEVER.	ERYTHEMA INFECTIOSUM.
CONTAGION	Apparently varies in epidemics. Direct contact. Possibly from fomites, not through the air.	Highly contagious. By direct contact. By fomites. Through the air.	Marked. By direct contact. By fomites.	Feeble. Usually by direct contact.
INCUBATION.	Variable average 1 to 3 weeks.	Average 9 to 14 days.	Average 1 to 6 days.	Average 6 to 14 days.
PRODROMES.	Slight and of short duration. Occasionally a day or two of malaise.	3 to 4 days. Drowsiness and catarrhal symptoms.	Short or wanting —onset usually sudden.	Very slight and of short duration.
KOPLIK SPOTS.	None.	Present in 90 or 95 % of cases.	None.	None.
VOMITING.	Rare.	Occasional.	Common.	Uncommon.
FEVER.	Slight—average 1 to 2 days, sometimes for 4 days, seldom more than 101 to 102 degrees.	Marked high curve lasting about a week, average from 102 to 104 degrees.	High fever lasting about a week, averages 104 to 105 degrees.	Little or none.
CATARRHAL SYMPTOMS.	Slight.	Marked.	Absent.	None.
TONGUE.	Slight coat, nothing characteristic.	Tongue coated, that of any fever.	Strawberry, later mulberry tongue.	Sometimes slightly coated.
THROAT.	Small punctiform red spots over uvula and palate. Pharynx slightly reddened.	Moderate pharyngitis and redness of mucous membranes.	Usually a severe angina.	Sometimes very slight sorethroat at onset.
DIARRHŒA.		Frequent.		
LYMPH NODES.	General enlargement, especially of post cervical nodes.	Postcervical, postauricular, and submaxillary nodes enlarged.	Depends on extent of throat involvement, glands at angle of the jaw involved.	Not enlarged.
PULSE.	Varies with fever.	Varies with fever.	Very rapid.	Normal.
ALBUMINURIA.	Rare and slight.	Rare.	Common.	None.
ERUPTION.	Begins on face, spreads to neck and breast then to arms, legs and feet. Is fading from older parts while spreading to new. Two forms—common form, morbilliform, small, slightly elevated papules, discrete, sometimes confluent, more rarely scarlatiniform, lasts 2 to 4 days or less, color rose-red but this varies.	Begins on face, spreads gradually over entire body. Covering it by the second or third day, consists of small papules arranged in crescentic groups, these are confluent in places, lasts 4 to 5 days. Is deep red, often purplish.	Begins on neck and chest spreads slowly over entire body —maximum about the fourth day. Does not affect lips. Consists of small punctate spots or a diffuse blush, disappears on pressure, lasts about a week. Intense red color.	First on face as symmetrical, rose-red blush, for the most part sharply defined and resembles erysipelas. It is hot to the touch but not sensitive and it does not itch. The second day it spreads to the body and extremities, small discrete crescentic patches over the body and sparingly on the inner and flexor surfaces of limbs. Marked map-like eruption on outer and extensor surfaces. Begins to fade on face in 4 or 5 days. Lasts altogether 6 to 10 days.
DESQUAMATION.	Slight and branny.	Branny.	Marked in flakes and large pieces.	None.
CONVALESCENCE.	Rapid, no complications.	Slow, frequent complications as pneumonia. Later other infectious diseases as tuberculosis.	Slow, complications frequent as nephritis, otitis media, etc.	Rapid, no complications.

were a marked feature of the Malta epidemic. Cuomo reports relapses in all of his 90 cases, but his epidemic differs in many particulars with the generally accepted clinical picture of rubella. Griffith reports relapses on the eleventh and twentieth day and Edwards on the fourth and twentieth.

Diagnosis.—The polymorphous rash, the eruption on the uvula and soft palate, and the glandular enlargement with an absence of other symptoms, are the most important features. Rubella occurs in epidemics, and sporadic cases are to be looked on rather as measles or scarlet fever. It must be distinguished from drug rashes, especially that from copaiba. The so-called roseola simplex due to heat or indigestion and so common in infancy must not be confounded with it. Dukes has called attention to a rash caused by handling certain varieties of caterpillars, which might be mistaken for rubella. Comby gives the absence of the diazo reaction as one of the signs in differentiating scarlet fever, and the absence of Koplik spots and catarrhal symptoms is of especial value in excluding measles.

Prognosis.—This is almost invariably good. Fatalities are so exceptional as to be regarded as due to the accidental association of some other disease. Epidemics have been reported with a considerable mortality, as one by Edwards in which it was 4.5 per cent.

Treatment.—This is very simple. If the child has fever he should be kept in bed; but if there is no fever and the child feels well there is no danger in allowing him to be about. Small doses of spirits of nitrous ether may be given if there is fever, and phenacetine, with small doses of codeia, if there is much restlessness and nervousness. As a rule no treatment whatever is required.

THE FOURTH DISEASE.

In July, 1900, Dr. Clement Dukes, physician to the Rugby School, published a paper in the *Lancet*, describing an infectious disease which he called "The Fourth Disease." This affection has been discussed at considerable length by numerous observers. The incubation period was about the same as that of German measles, nine to twenty-one days. Prodromes were usually absent, but malaise and some sore throat were sometimes present at the onset of the rash. The rash appeared rapidly and covered the body in a few hours. Dukes does not mention whether it appeared on the face or not. The color of the rash was said to have been brighter than that of scarlet fever and was followed sometimes by slight and sometimes by marked desquamation. There was some glandular enlargement. The temperature was usually not over 101°, but in one instance it was 104° F There were no sequelæ and the attack did not protect the individual against either scarlet fever or rubella. For further information the reader is referred to Dukes's original article and to a discussion of the subject by Ker.[1] The latter renders what he calls the Scottish verdict of "not proven," which is very generally accepted.

[1]Ker, *The Practitioner*, February, 1902, p. 135.

ERYTHEMA INFECTIOSUM.

Definition.—Erythema infectiosum is a feebly contagious disease of childhood characterized by a maculopapular, rose-red rash, especially marked on the face and the external surfaces of the extremities, and by slight or no subjective symptoms.

Historical.—This was first described as a separate clinical entity by Escherich, in 1896, and the name which he adopted was suggested by Stricker, in 1899. It has not been reported in America up to date but there have been numerous accounts of epidemics in Austria and Germany.

Etiology.—The exciting cause is unknown, and no organism has been described. The disease usually occurs in epidemics, most frequently in spring and summer, and children between the ages of four and twelve years are most often affected. It is but feebly contagious, and close contact is required to communicate the disease. An attack does not protect from measles, scarlet fever, or German measles.

Pathology.—No autopsies have been reported, and the only lesions known are erythema and occasionally slight pharyngitis.

Symptoms.—The incubation period has been from six to fourteen days in the cases in which accurate observations could be made. There may be slight prodromes, as malaise and sore throat, but usually the appearance of the eruption is the first sign of the disease. On the first day the rash appears on the face and is described as a rose-red efflorescence which covers the cheeks, extending to the nasolabial folds in front, to the temples above, and laterally as far as the angles of the jaw. Over this area the rash is confluent, slightly raised above the surface, and for the most part sharply outlined, although in places it may fade gradually into the healthy skin. The general appearance is that of erysipelas, but whilst the skin is hot to the touch it is not sensitive and does not itch. There is no subcutaneous hemorrhage on pinching the skin. The rash disappears on pressure but reappears quickly when the pressure is removed. On the following day the eruption extends to other parts of the body, and on the forehead and chin there are discrete patches. It spreads slowly downward, and on the trunk there are discrete somewhat crescentic patches, from an eighth to half an inch long and suggesting measles, which may also at times be wheal-like, resembling urticaria. The eruption is marked on the extensor and outer surfaces of the arms and legs, and about the elbows and buttocks it may be confluent. Over the extremities the rash is morbilliform and the spots run together, forming map-like areas, which are especially marked when the eruption begins to fade. Shaw suggests that it resembles lace work. The color varies from a rose-red to a brownish-red. The hands and feet are the last places to be affected, and the mucous membranes are not involved. The eruption fades first from the face after four or five days, and a few days later disappears from the body. In all it lasts from six to ten days, and in some cases may disappear and then reappear after a short time. There is no subsequent pigmentation or desquamation.

There are practically no subjective symptoms, although there may be a very slight sore throat at the onset and the tongue may be somewhat coated. There is no glandular enlargement.

Diagnosis.—This depends largely upon the recognition of the rash, and is not difficult. The following are the most striking points of difference:

Scarlet fever—Marked constitutional symptoms, high fever, strawberry tongue, angina, and a uniform rash. *Measles*—Marked constitutional symptoms, fever, catarrhal symptoms, and Koplik spots. *Rubella*—Enlarged lymph nodes, especially the posterior cervical, and the presence of the eruption over the soft palate and the uvula. *Drug Rashes*—The history of taking drugs. *Urticaria*—The itching. *Erythema exudativum multiforme*—This begins on the hands and feet, becomes vesicular, lasts for weeks, and is attended by marked constitutional symptoms. Erythema infectiosum is not to be compared with the so-called "fourth disease," in which there is said to be a scarlatiniform rash making its appearance in a few hours and often followed by desquamation.

Prognosis.—This is favorable, as there have been no fatal cases reported, and there are neither complications nor sequelæ.

Treatment.—There are no indications for treatment.

CHAPTER XIV.

DIPHTHERIA.

By JOHN H. McCOLLOM, M. D.

Synonyms.—Angina maligna; cynanche contagiosa; cynanche suffocativa; cynanche tonsillaris; diphtheritis; diphthérite (Fr.); Diphtherie (Ger.).

Definition.—An acute infectious and contagious disease, generally of the air passages, characterized by the presence of a patch of dirty-white or grayish membrane, cultures from which show a bacillus known as the Klebs-Loeffler or the *Bacillus diphtheriæ*. The terms membranous croup, suffocative catarrh and angina maligna are misnomers and should not be used, because they do not convey any idea of the etiology of the disease. It is important to emphasize that diphtheria at the outset is a local manifestation and that the constitutional symptoms which occur later are due to the absorption of the toxin generated by the specific organism.

History.—Diphtheria is by no means a disease of modern origin. In the year 111 A. D., Aretæus wrote regarding a disease of the air passages, which he termed the Egyptian ulcer. He described the train of symptoms which we now recognize as diphtheria. Hippocrates and Galen seemed to have recognized diphtheria, particularly Galen, because he is said to have performed laryngotomy. From time to time epidemics of this disease have been the subject of medical essays, and early medical literature is full of theories regarding diphtheria and the proper treatment of it.

At different times in the early history of Boston there were epidemics of this disease, particularly in 1735 and 1736. At this time Dr. Douglass, of Boston, wrote a pamphlet on "Angina Ulcusculosa," which must have been diphtheria. The common name of the disease was "Throat Illness or a Plague in the Throat." The epidemic was so general and caused so much alarm that the selectmen had a conference with the leading practitioners of that time regarding measures to prevent its spread.

In 1749, Chomel wrote regarding a gangrenous disease of the throat which we should now recognize as diphtheria. Of 8 patients ill with the disease, 6 died. The account which he gives of the clinical symptoms answers perfectly the description of malignant diphtheria. In one patient who recovered there was marked palatal paralysis and strabismus. In 1765 Francis Home,[1] of Edinburgh, published a pamphlet entitled, "An Inquiry into the Nature, Cause and Cure of Croup." The word croup at that time was the term given to diphtheria. Dr. Home gives an accurate description of twelve cases which we would now term diphtheria. The account of the autopsies is extremely interesting. For instance, he says: "When the trachea was opened the whole internal surface was covered with a membrane

[1]Francis Home, M. D., *An Inquiry into the Nature, Cause and Cure of Croup*, Edinburgh, 1765.

for three inches downward from the glottis. This membrane was complete all around, did not adhere to the trachea, and came off in the shape of a hollow tube. The natural coats of the trachea seemed entire and not ulcered. The substance of the lungs was quite sound; but the vesicles of the left lobe were filled with yellow, thick pus, which sunk in water. The new-formed membrane had some degree of tenacity, and when steeped in milk-warm water for two days did not dissolve, but preserved some degree of cohesion. No fibres could be observed in it." In this pamphlet there are many accounts of similar autopsies.

In 1771 Dr. Samuel Bard, of New York, wrote an elaborate article on the "Cause, Nature and Treatment of Suffocative Angina." His description of the disease which we know as diphtheria is extremely vivid, but his knowledge of the etiology is somewhat vague.

In 1821 Bretonneau, who first used the term diphtheria, published his exhaustive paper on this disease but his work apparently was not appreciated by the profession, and in many instances there was marked opposition to his theories and deductions. In the light of our present knowledge, however, Bretonneau's work was a distinct advancement. Although his opinion regarding the etiology of the disease is not in accord with present ideas yet the careful manner in which he described the clinical symptoms makes his investigations of the greatest importance.

In 1847 there was an outbreak of sore throat in England which was traced to Boulogne and was known as the Boulogne sore throat. There is no doubt that this disease was diphtheria. Since that time diphtheria has been more carefully studied and more generally recognized.

The pamphlet of John Ware,[1] published in 1850, although written in 1842, is a valuable contribution as far as the clinical appearances of what he termed membranous croup and what we should call diphtheria are concerned. Dr. Ware makes a careful distinction between membranous croup and spasmodic croup.

Etiology.—Many different theories have been advanced regarding the etiology of diphtheria. Soil-moisture, sewage gas, imperfect drainage, poor hygienic surroundings, overcrowding, have been supposed to be important factors in causing the disease. It is absolutely certain that, although these conditions may have a predisposing influence, they never of themselves can originate diphtheria.

It was not until 1883, when Klebs demonstrated a small bacillus in the false membrane of diphtheria that the etiology was placed on a scientific basis. Loeffler in 1884 isolated and cultivated this organism; hence the term Klebs-Loeffler bacillus. Darier, in 1885, independently arrived at similar results. Roux and Yersin found this bacillus in all cases of diphtheria. It is a short rod, straight or slightly curved with a diameter of 0.5 to 0.8μ and from 2 to 3μ in length. This organism grows on all the usual culture media. It is aërobic, non-motile, and non-liquefying; it grows characteristically on Loeffler's blood serum. This culture medium should be neutral or very slightly alkaline. If it is acid or strongly alkaline the organism will not grow satisfactorily. The bacillus of diphtheria grows more abundantly at the temperature of the body than at room temperature. Cold inhibits its growth but does not destroy its vitality. Under suitable conditions its vitality may

[1] Dr. John Ware, "Contributions to the History, Diagnosis and Treatment of Croup," *Boston Medical and Surgical Journal*, 1850.

PLATE XVII

FIG. 1

FIG. 2

FIG. 3

Fig. 1.—Slide prepared from a culture from a non-diphtheritic throat.
Fig. 2.—Diphtheria bacilli stained by Loeffler's method.
Fig. 3.—Diphtheria bacilli stained by Neisser's method.

FIG. 4

FIG. 5

FIG. 6

Fig. 4.—Diphtheria bacilli stained by Hunt's method.
Fig. 5.—Diphtheria bacilli of the short variety.
Fig. 6.—Diphtheria bacilli of the long variety.

be retained for a long time, but as it has no spores it can be easily destroyed by different germicides. Welch and Abbott found the thermal death-point to be 58° C. for ten minutes, and other observers have arrived at similar results.

The bacillus of diphtheria can be stained with the common aniline dyes, but Loeffler found that an alkaline methylene blue was the most satisfactory stain. The composition of this is as follows: saturated alcoholic methylene blue 30 parts, and a watery solution of potassium hydrate (1 part to 10,000) 100 parts. (Plate XVII.)

Neisser's differential stain is of great use in deciding the character of doubtful bacilli. When the staining is properly done the pole granules are of a deep-blue color and can be very distinctly seen when examined under the microscope. The body of the organism is stained a light brown. So far as is known, no organism except the diphtheria bacillus presents the peculiar appearance just described.

Hunt's method of staining is as follows: first, stain in a saturated aqueous mythelene blue one minute without heating; second, wash and dry; third, cover with a tannic acid solution, 10 per cent., for one minute; fourth, wash; fifth, stain in an aqueous methyl orange solution one minute; wash and dry. When a preparation is stained in this way and examined under the microscope, the pole granules are distinctly seen as small dark-blue points and the body of the organism is of a light-orange color. These differential stains are of great assistance in deciding the character of bacilli which are often mistaken for the organism of diphtheria.

The diphtheria bacillus is not always of the same size. There are two varieties, described as the long and the short variety. This change in appearance is due, in some instances, to the length of time that the culture has been in the incubator, and in other instances to the stage of the disease when the culture was taken. Some observers have inclined to the opinion that the degree of virulence depended to a certain extent on the length of the bacillus. These observations conducted in the laboratory have not been borne out by clinical experience; the appearance of the organism under the microscope conveys no idea regarding the severity of the attack of diphtheria in the patient from whom the culture was taken.

Pathology.[1]—The essential lesions may be divided into two kinds: local lesions, characterized by the formation of a membrane, and due to the immediate presence of diphtheria bacilli and the direct action of the strong toxic substances secreted by them, and general or systemic lesions due to the absorption of these toxic substances and their passage in a more dilute form in the lymph along the lymph vessels, and in the blood throughout the general vascular system. In addition there often are lesions of a third kind due to secondary infections by other bacteria, which may complicate both the local and the systemic changes produced by the diphtheria bacillus.

The local lesions begin most frequently in the fauces (tonsils), the larynx or the nares, rarely in the conjunctiva. From these primary foci the process often extends to the uvula, the pillars of the fauces, the posterior wall of the pharynx, the trachea and lungs, or to the accessory sinuses of the nose. More rarely it extends to the œsophagus, the tongue, the skin around the

[1]This section was written by F. B. Mallory, M. D., Associate Professor of Pathology, Harvard Medical School; First Assistant Visiting Pathologist, the Boston City Hospital.

nose and mouth, the conjunctiva through the lachrymal ducts, or to the middle and external ear through the Eustachian tube and a perforated membrana tympani. Still more rarely, diphtheria bacilli produce lesions in the stomach and duodenum, or are conveyed to the genitals (vulva, vagina, penis) and give rise to membrane formation there.

The distribution, extent, and intensity of the local lesions vary greatly in different cases. Statistics in regard to them should be based, so far as possible, on clinical observations rather than on postmortem findings, which represent conditions in fatal cases only: otherwise a false impression will be obtained. On the other hand, it is only by means of postmortem examinations that the extent of the distribution of local lesions can be determined in certain cases—stomach, accessory sinuses of the nose, etc.

The local lesions show in all situations essentially the same pathological processes; namely, degenerative changes in the epithelial cells and in the underlying tissues, combined with an abundant fibrinous exudation from the bloodvessels. As a result of these degenerative and exudative processes separately or combined, a membrane is formed on the epithelial surface affected.

The degenerative changes in the epithelial cells in the primary lesions vary greatly in extent and character, but those most noticeable are multiplication of the nuclei by direct division (an early change), necrosis of cells with hyaline transformation or with disintegration of the cytoplasm and fragmentation of the nuclei, and desquamation of cells. The hyaline transformation of cells may take place either before or after desquamation. Necrosis with fragmentation of the nuclei is always most evident in the mucous glands where it forms a pronounced and almost specific process. As a rule, the epithelium is absent beneath the membrane, although in places small masses of epithelium consisting of the lower layers of cells may be found, and occasionally the membrane may stretch over a considerable area of epithelium in which only the upper layers of cells are absent. The degenerative changes which take place in the tissues beneath the epithelium consist chiefly of necrosis of cells and of a hyaline fibrinoid change in the connective tissue and in the walls of the bloodvessels, but the process is not specific of diphtheria. Sometimes the lesion is extensive enough to affect striated muscle. Then some fibers show œdema, others a loss of the characteristic striations, while still others are changed into swollen, homogeneous, or reticulated refractive masses. Sometimes the muscle nuclei undergo direct division.

The inflammatory exudation is always marked. The fluid portion is apparently rich in fibrin factors, since, wherever it comes in contact with necrotic epithelial or other cells, it produces fibrin. As a result an abundance of fibrin is found on the epithelial surfaces and to a less extent in the underlying tissues. Its presence masks to some extent the degenerative changes in the cells and tissues. The cellular elements of the exudation consist at first chiefly of polynuclear and non-granular leukocytes, together with a larger or smaller number of red blood corpuscles, but in the later stages numerous lymphoid and plasma cells appear. Most of the leukocytes pass to the surface and are found chiefly in the meshes of the membrane, but the lymphoid and plasma cells usually remain in the underlying tissues.

The membrane which is so characteristic but not specific of diphtheria has received a great deal of study. Macroscopically it appears at first grayish-white in color, but may change to a dirty-gray, yellowish-gray, grayish-brown,

or almost black color. It may occur in isolated patches or as a continuous layer: as a thin pellicle or a thick membrane. It may be granular and easily broken up, or dense and elastic so that it can be removed in large patches. It is always more easily removed from the trachea than from any other situation. When the trachea is opened, the membrane often appears as a loose wrinkled mass lying in the lumen. Removal of the membrane from the trachea or larynx, even when it is thick and adherent, rarely leaves a loss of substance extending into the subepithelial connective tissue. The tissue beneath the membrane and in its vicinity is always intensely injected and often hemorrhagic.

Very thick masses of membrane may be formed by the constant addition of fibrinous exudation. In the later stages of the disease the membrane may disintegrate and be broken up into a mass of detritus, or it may be cast off as a whole by being elevated by an exudation beneath it. Microscopically two forms of membrane are recognized, the fibrinous and the hyaline. The fibrinous membrane often occurs in a pure condition, especially in certain situations such as the trachea; but the hyaline membrane usually, perhaps always, occurs in combination with the fibrinous.

The fibrinous membrane is characterized by greater friability than the hyaline. It is formed at first around cells which usually afterward disappear. The fibrin appears as a reticulum of which the fibers vary much in size and in which the spaces are rather large, more often oblong than round, and with the long diameter parallel with the surface. In the spaces are usually numerous leukocytes either well preserved or undergoing disintegration, but over mucous surfaces covered with pavement epithelium desquamated epithelial cells undergoing hyaline degeneration are often present. The fibrinous membrane is not always limited to the surface. It is often connected with masses of fibrin in the underlying tissues, and if these tissues, as not infrequently happens, undergo a hyaline fibrinoid change, they may lose their identity more or less completely and unite with the membrane to form a part of it. Such adhesions between the fibrinous membrane and the underlying tissues is more common over surfaces covered with pavement epithelium than in the trachea, where the thick basement membrane on which the epithelium rests usually prevents the membrane on the surface from uniting with the fibrin and hyaline transformed tissue beneath it.

The hyaline membrane is dense, firm, and elastic, and can be stripped off in large flakes. It is most often found on those surfaces which are covered with pavement epithelium, *e. g.*, the tonsils. It is much denser and more refractive both in the stained and in the unstained condition than is ordinary fibrin, and stains more or less imperfectly with the fibrin stain. Microscopically it appears as a reticular structure of which the beams are homogeneous, coarse, and of a uniform thickness. The spaces enclosed by the reticulum are small and vary but little in size; they may be angular or round. Few cells are enclosed in the spaces. The hyaline membrane arises in two ways; by fusion of hyaline degenerated cells with disappearance of the nuclei, or by fibrin forming around and fusing with cells which undergo hyaline change. The cells which undergo this hyaline transformation usually are epithelial cells, but leukocytes may undergo the same change, in which case the spaces in the reticulum are smaller.

Diphtheria bacilli are found, usually in clumps of various sizes, chiefly on the surface of the membrane, but they occur also to some extent in the

necrotic tissue, and rarely enclosed in leukocytes and necrotic epithelial cells. While the diphtheria bacillus is confined for the most part to the local lesions, it sometimes gains access to the general circulation and gives rise to a septicæmia. Very rarely it gives rise to localized lesions as a result of this septicæmia, for example, acute endocarditis. For the most part it remains in the general circulation, and simply increases the amount of toxins in the blood.

The local lesions produced by the diphtheria bacillus are often complicated by secondary infections with other bacteria, especially with the *Streptococcus pyogenes*. Such secondary infections may result in extensive necrosis and ulceration, or even lead to gangrenous processes in the throat or extensive sloughing of the tissues of the neck.

The lesions of the lungs, although usually due to secondary infections, must be considered in connection with the local lesions, partly because they often are due in some measure at least to the immediate presence of the diphtheria bacillus, partly because the systemic lesions in the lungs are of little significance. The lesions of the lungs are the most frequent and serious which accompany diphtheritic infection and many cases are so extensive that death may be considered as due rather to the condition of the lungs than to the throat affection. While the antitoxin treatment may lead to the disappearance of a diphtheritic membrane, it cannot influence a streptococcus or pneumococcus infection of the lungs.

The most common lesion is bronchopneumonia. The term implies both the manner in which infection takes place and the relation of the foci to the bronchi. It may be limited to single acini, to lobules, or to groups of lobules. There is but little lateral extension of the infection through the walls of the alveoli or the bronchi into the surrounding air spaces. Acute inflammation of the larger bronchi usually accompanies it, but is not constant. Atelectasis varying in extent is very commonly present. The same is true of emphysema. Cases of extensive confluent bronchopneumonia occur.

The character of the exudation varies greatly. It may be fibrinous, hemorrhagic, serous, or almost entirely cellular. The cells in the exudation are partly polynuclear leukocytes, and lymphoid and plasma cells, partly cells derived from proliferation of the lining epithelium. Cellular infiltration of the interstitial tissue and proliferation of the connective tissue cells are common. Necrosis leading to abscess formation is a frequent complication. Streptococci, pneumococci, and diphtheria bacilli are found with the different forms of exudation and with necrosis and abscess. The streptococcus and pneumococcus must be considered the principal agents in producing the lung infection. Diphtheria bacilli are frequently found, and may be the cause of bronchitis with membrane formation, of purulent exudation, of bronchopneumonia, necrosis, and abscess. They are often found in the lung in much greater numbers than in any other situation, and there may be but little change in the tissue around them.

The systemic lesions due to the absorption of the diphtheria toxins are partly degenerative, partly exudative, and partly proliferative in character. They are more or less characteristic, but are not specific. Other acute infectious diseases may show similar pathological changes. Some of the systemic lesions are of little clinical significance, but others, especially those occurring in the heart, the kidneys, and the nerves, are often of vital importance. The systemic lesions due to the toxins of the diphtheria bacillus are

often complicated by the toxins absorbed from other bacteria which invade the primary lesions, or from those bacteria which give rise to secondary lesions in the lungs.

In the heart, so-called fatty degeneration of the myocardium is one of the most common lesions; it is found especially in the severe cases of short duration. It varies in extent, at times affecting the myocardium generally, at times occurring in foci. The fat may appear in the form of fine granules or of large globules. The fatty degeneration accompanies and seems to precede the other more advanced forms of degeneration which lead to the complete destruction of the muscle fibers. These more marked changes are the destruction of the sarcous elements, which become swollen, broken up, and converted into hyaline masses, and the formation within the cells of large vacuoles, which differ in size and by their irregularity of shape form the fat vacuoles. These degenerations may be so extensive as to account fully for the impairment of the heart action observed clinically. No bacteria are found in connection with these degenerative changes; like most of the systemic lesions they are due to the influence of the toxic substances circulating in the blood. The mural thrombi which not infrequently occur in cases of rather long duration are due to the extension of the primary necrosis of the myocardium to the endocardium.

In addition to these degenerative lesions two forms of acute interstitial myocarditis occur. In one there are focal collections of plasma and lymphoid cells in the connective tissue; this lesion may be accompanied by degeneration of the myocardium, but apparently is not dependent on it. The condition is analogous to that occurring in the kidneys and termed acute interstitial non-suppurative nephritis. In the other form of acute myocarditis there occurs a proliferation of the connective tissue cells, which is secondary to the degeneration of the muscle fibers. It is probable that this lesion may lead to extensive formation of connective tissue and thus be the cause of some cases of chronic myocarditis.

Lesions of the spleen play but a slight part. Macroscopically the spleen does not differ from normal, except that the lymph nodules usually are more prominent. The most obvious lesion, microscopically, consists of the formation of foci of epithelioid cells in the lymph nodules. These cells are of the same character and are formed in the same way as those in the lymph nodes. They are phagocytic, and the nuclear detritus found in them comes chiefly from the lymphoid cells. A frequent lesion is hyaline degeneration of the walls of the arteries, which is more common in the vessels of the spleen than elsewhere. Sections stained for fat show numerous droplets in the hyaline areas. In the later stages of diphtheria numerous plasma cells are found in the spleen, which probably plays an important part in their formation.

Occasionally, as in scarlet fever, accumulations of lymphoid and plasma cells are found in the intima of veins beneath the lining endothelium. In some cases the cells are uniformly distributed; in others they form nodular projections into the lumen of the vessel.

In a few instances a diphtheritic membrane is formed in the stomach. It usually occurs in limited areas, but may cover the whole surface. As a rule it is fibrinous but the hyaline variety has been described. The membrane is always attached to a surface deprived of epithelium, but may extend out some distance over apparently normal mucous membrane. Very rarely a diphtheritic membrane may be present in the duodenum. Below this point

but little macroscopic change is found in the intestine beyond swelling of the lymphoid tissue, especially of the lymph nodules. These show the same changes as the lymph nodules in the lymph nodes elsewhere in the body and in the spleen

The lesions in the liver are not characteristic and do not differ from those found in other acute infectious diseases They are due to the effect of soluble toxic substances and not to the presence of diphtheria bacilli. The most common lesions are a general degeneration (albuminous and fatty) of the liver cells, and more rarely necroses, which are limited chiefly to the centre of the lobules.

In the kidneys a variety of lesions may be found, either degenerative, exudative, or proliferative in character. The different forms of lesions may occur separately or in various combinations. The degenerative changes in the epithelium consist of cloudy swelling, the deposition of fat droplets, and the transformation of the cytoplasm into hyaline droplets.

Acute interstitial changes, generally included under the term acute interstitial non-suppurative nephritis, are fairly common. They consist of the infiltration of the connective tissue, chiefly in the cortex, with lymphoid and plasma cells. Occasionally polynuclear leukocytes and phagocytic cells are associated with them. The cellular infiltration is usually focal and is always most marked in three situations: at the base of the cortex adjoining the pyramids, just beneath the capsule, and around the glomeruli. In some cases the foci are confined to the pyramids. These changes in the interstitial tissue are always accompanied by the crowding of the bloodvessels, especially in the upper part of the pyramids, with these same cells which emigrate out into the tissues. In the most marked cases of this lesion the kidneys are greatly enlarged and may weigh more than four times the normal. The capsule is distended and thin, and on section often separates spontaneously from the surface, which is pale and of an opaque grayish color, mottled with irregular, more hyperæmic areas. The stellate veins of the surface are enlarged, and punctiform hæmorrhages are often found in their vicinity. On section the normal markings are obliterated, and the contrast between pyramids and cortex is indistinct. The increased size is due chiefly to the swelling of the cortex. In the less marked cases there are opaque areas, often in lines corresponding to the course of the tubules, due to the interstitial infiltration.

Acute glomerulonephritis is much less common than the interstitial form, and the lesion is chiefly of the intracapillary type due to proliferation of the endothelial cells lining the capillaries of the glomerular tuft. Slight hemorrhages in the kidney occur occasionally, but hemorrhagic nephritis with escape of blood into the tubules is very rare.

The lesions in the lymph nodes are among the most constant changes produced in diphtheria, and are most marked in cases of great intensity in which death takes place early. They are most marked in those lymph nodes, *e. g.*, the cervical, which are nearest the primary local process and, hence, receive the diphtheria toxins in the most concentrated form. They are least marked in those to which the toxins penetrate in greatly diluted form through the circulation. Macroscopically the most affected lymph nodes are enlarged, soft, and hyperæmic. In some cases there is extensive hemorrhage, and diffuse and circumscribed necroses are not uncommon. There are other lesions distinctive of diphtheria, although they may be found in other in-

fectious diseases, which consist of the formation of foci which are very similar to miliary tubercles. In these foci there is a combination of proliferation, phagocytosis, and degeneration. Proliferation of the endothelial cells lining the reticulum gives rise to the formation of larger cells resembling the epithelioid cells of the tubercle. These cells devour the lymphoid cells of which the nuclei in dissolving undergo fragmentation and appear as nuclear detritus. The phagocytic cells themselves often undergo necrosis with fragmentation of their own nuclei. Caseation is never produced, and no giant cells are formed, but the necrotic cells may fuse and undergo a hyaline change.

In the tonsils local primary lesions of the surface with extension to the crypts are combined with the lesions of the underlying lymphoid tissue. In the thymus gland nothing is found beyond degeneration of lymphoid cells.

In the bone marrow the chief lesion consists of a hyperplasia of plasma cells which enter the general circulation and may emigrate into various organs, more especially the kidneys, giving rise to interstitial changes. This process is not peculiar to diphtheria.

No changes have been observed in the pancreas, adrenals, thyroid and salivary glands, pituitary body, testicles, and ovaries, in diphtheria cases.

In the nervous system various degrees of fatty degeneration frequently occur. The process seems to begin almost invariably in the myelin sheath. The myelin breaks up into granules, droplets and very irregular figures. The change in the axis cylinder consists chiefly of swelling which is often irregular, so that it presents a beaded appearance, and as it swells is stains very faintly, so that when the myelin sheaths have undergone marked fatty degeneration, the axis cylinders usually can not be distinguished. These changes occur not only in the peripheral nerves, but also in the white matter of the brain and cord. They are of great clinical importance because they are the cause of the most important sequel of diphtheria, paralysis.

The skeletal muscles, like the nerves, often show various degrees of fatty degeneration. In fact, the process in the two tissues seems to occur at the same time and to be of equal intensity. The muscle fibers may be affected uniformly, or only single fibers may contain fat droplets.

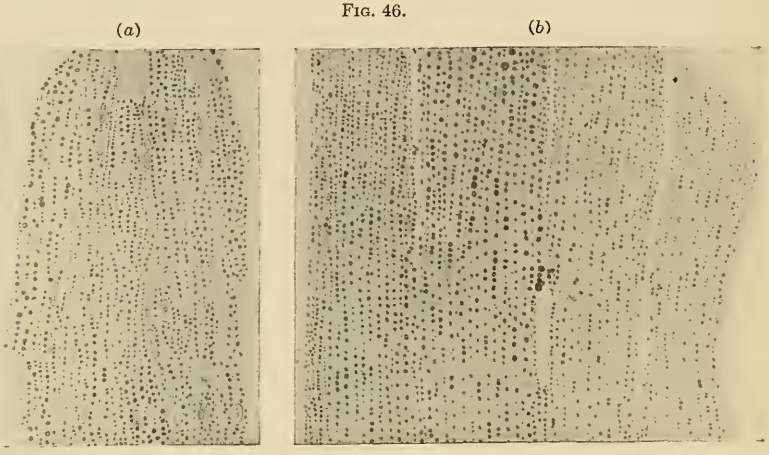
These degenerative changes in the nervous system and in the skeletal muscles, together with the lesions in the heart, account for the slow recovery and long persistent weakness in many patients after an attack of diphtheria. Similar changes of a milder type are probably usually present.

Symptoms.—The incubation period is from twenty-four hours to three days. Diphtheria differs from other infectious diseases in the period of incubation, as the process of infection is similar to that of a dissecting wound. The organism finds access through an abrasion generally of the mucous membrane, in just the same way as infection is produced from the prick of a needle at an autopsy or a scratch during dissection.

In discussing the symptoms it is important to make a somewhat artificial division of the different forms of diphtheria. It is well to emphasize that diphtheria at the outset is a local disease and that the constitutional symptoms depend absolutely upon the amount of toxin generated by the specific organism. The different forms are: pharyngeal, which is the most common; laryngeal, incorrectly termed membranous croup; nasal; cutaneous; diphtheria of the lungs; diphtheria of the eye. Pharyngeal diphtheria commences with a feeling of chilliness, not amounting to a distinct rigor, head-

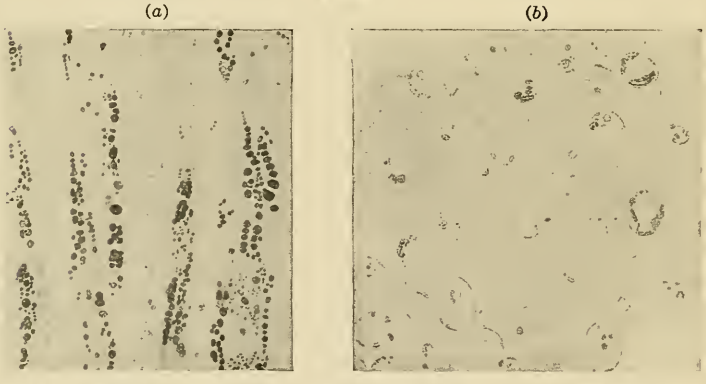
ache not particularly severe, and a rise in temperature not particularly marked. The soreness of the throat at the outset is not very severe, but at the end of about twelve hours becomes more pronounced, and if the fauces are examined there will be found a peculiar congestion of the tonsils and adjacent parts which has a distinctive—almost purplish—hue. At the end of twenty-four hours patches of membrane of a dirty-white color can be seen. At the end of thirty-six hours, or twenty-four from the appearance of con-

FIG. 46.



Fatty degeneration (*a*) of heart muscle, (*b*) of skeletal muscle

FIG. 47.



Fatty degeneration of nerve, (*a*) in longitudinal section, (*b*) in cross section.

gestion in the throat, the membrane extends very rapidly and covers the tonsils, the uvula, and the hard and soft palate. Dysphagia now becomes a prominent symptom; the temperature has risen two or three degrees; prostration commences to be marked. The membrane, which has been quite thin, now becomes very thick and can not be removed from the subjacent parts without difficulty, and if removed leaves a bleeding surface. In the very early stage of the membrane formation the exudate can be removed with little difficulty and without bleeding. Failure to recognize this fact has

frequently led to errors of diagnosis. The breath of the patient at the end of forty-eight hours commences to have a strong septic odor. After seventy-two hours the pulse has a peculiar soft feeling, and the patient may be actively delirious, or lie in an apathetic state. After the membrane has begun to form it increases very rapidly, and in a severe attack at the end of three days the process has been ended by the death of the patient. Only twelve hours sometimes elapse from the appearance of a small patch of membrane until the tonsils, uvula, and soft and hard palates are covered with it. If irritant gargles are used at the outset, the membrane forms much more rapidly, because, owing to the inflamed condition of the mucous membrane, the epithelium is removed by these agents, and a fresh field is offered for the growth of the organism. Laboratory experiments have proved that the bacillus of diphtheria will not grow on intact mucous membrane, and this explains its rapid advance where irritant gargles have been used. If the patient lives long enough the septic odor increases in intensity and after a time the membrane may exfoliate. A profuse sanious discharge from the nose now appears; there may be hemorrhage from the mucous surfaces; spots of ecchymosis appear on the body; the patient is in a cold clammy perspiration; the pulse is rapid and extremely feeble; he can be roused with difficulty, and when roused does not answer questions coherently. The urine is scanty and loaded with albumin. Nourishment is refused partly on account of dysphagia and partly because of inability to swallow from lack of strength. Death supervenes from the absorption of the toxin, and the albuminuria is caused by the same agent. The temperature is not specially elevated in diphtheria unless there is some complication. If the membrane is not very extensive it may be exfoliated at the end of seven or eight days, and may re-form. If, however, it does not, the patient may commence to improve for a time and the mucous membrane may assume a normal appearance. The physician feels gratified to find the patient improving, when suddenly the patient has an attack of vomiting, passes into a state of collapse and dies in from six to eight hours. Sometimes at the end of three or four weeks, when everything seems to be progressing favorably, the pulse rate will fall to 30 or 40, or even lower, and the patient, without any complaint of discomfort, will gradually sink and die. The effect of the toxin on the heart is to be always borne in mind in every attack, no matter how mild. A patch of membrane the size of a thumb-nail on the tonsil may generate sufficient toxin to cause death. Palatal paralysis is a very constant symptom in untreated cases. The writer has observed many cases of sudden death in which the only cause could have been an attack of diphtheria so mild that no physician was called until the patient was in *articulo mortis*. The knee-jerk is very frequently absent for some considerable time after an attack. The muscles of accommodation of the eye are frequently paralyzed. Strabismus and double vision are frequent symptoms. Paralysis of the extremities often occurs. The patient is unable to walk and is sometimes unable even to lift his head. He lies in a peculiar position in bed, which can hardly be described, but must be seen to be appreciated.

The symptoms of laryngeal diphtheria are essentially different from those of pharyngeal diphtheria. The attack begins with a hoarse brassy cough, a moderate rise in temperature, and a certain feeling of lassitude. If the fauces are examined, no membrane, in uncomplicated cases, can be seen. The general condition seems to be fairly good. At the end of twenty-four

hours the dyspnœa has increased and the metallic cough is a prominent symptom. Thirty-six hours later there is marked substernal and supraclavicular retraction. The patient is extremely restless and starts up in bed, clutches at the throat, and gasps in the endeavor to get air into the lungs. The *alæ nasi* will dilate and contract. Cyanosis now appears and it is impossible for the patient to get any rest. The substernal retraction is extremely marked in young children. In adults it is not so great, because the thoracic walls are so rigid that they prevent retraction to a certain extent. Supraclavicular retraction, however, is always present in adults as well as in children. Rigidity of the sterno-cleido-mastoid muscles is always present, both in adults and children; it is of great significance in the early stage of laryngeal diphtheria and should be a warning to the physician.

The train of symptoms just described is not present in spasmodic croup or in dyspnœa due to pneumonia or heart disease. The mistake is frequently made of failing to recognize the gravity of the symptoms at the outset. The laryngitis of a commencing attack of measles is very frequently mistaken for laryngeal diphtheria, and *vice versa*. A careful examination ought to prevent this mistake in the majority of instances. As time goes on the condition becomes more and more critical. The dyspnœa increases, the cyanosis becomes more marked, the substernal retraction increases, the patient becomes more exhausted, and death ends the scene. It sometimes happens that twelve hours before death, the dyspnœa is not so marked, simply from the fact that the patient is exhausted. This is a description of a typical case of laryngeal diphtheria, which, if not relieved by operative interference or by treatment, is one of the most distressing sights that a physician can see. Any one who has seen the congestion caused by diphtheritic membrane on the tonsils can readily understand how a small patch of membrane situated on the vocal cords or below them may cause sufficient swelling to occlude the glottis, the opening in which, particularly in children, is so small that a limited amount of œdema is sufficient to interfere with respiration. This explains why in many instances no membrane is seen in laryngeal diphtheria. All patients with laryngeal diphtheria without operative interference do not die, but a vast majority do. In laryngeal diphtheria the process extends very frequently to the bronchi, and often invades the smallest ramifications. Laryngeal diphtheria and pharyngeal diphtheria in many instances are associated, and the process extends from the pharynx to the larynx. Sometimes the uvula will be the only seat of the membrane, and from there it extends to the larynx.

Nasal diphtheria may be very severe or mild, depending upon the situation of the membrane. If the disease is situated in the posterior nares there may be great constitutional disturbance. If the condition of the tissues in this locality is borne in mind, it can be understood that the toxin generated is very readily absorbed and causes death from its effect on the heart. Many patients die from unrecognized nasal diphtheria because no membrane is seen and the first indication of serious trouble is rapid action of the heart, or in some instances there may be a slow pulse and the physician is often unable if he does not have the idea of nasal diphtheria in mind, to explain the symptoms. If the membrane forms in the anterior nares, the probability of absorption is reduced to a minimum and there is usually very little constitutional disturbance. The importance of the latter type is the danger of infection. Many serious outbreaks of diphtheria are due to individuals who have a

profuse discharge from the nose without any constitutional disturbance. This is not a theoretical statement, but the result of experience. Every profuse discharge from the nose, particularly if there is any excoriation about the nostrils, should be looked upon with suspicion and cultures taken. If adenoids are to be removed cultures should always be taken before the operation is performed, for it very frequently happens that a child who has a profuse nasal discharge, immediately after the removal of adenoids or ablation of the tonsils has a severe attack of diphtheria. If the operation for cleft palate is to be performed, it is still more important to take cultures, because, if there are any diphtheria bacilli in the nasal discharge, this organism is sure to grow upon the cut surfaces, and the patient not only has an attack of diphtheria, but the edges of the wound slough and render a second operation much more difficult.

Cutaneous diphtheria, as a rule, is not serious, as the membrane does not extend owing to unsuitable conditions. This does not apply to those cases where there is an abrasion such as a bite on the finger of the operator during intubation, for, in these fatal results have followed. It is not an uncommon thing for a female child to carry the infection from the nose to the vulva. An attack of diphtheria of the vulva is frequently attended with marked constitutional disturbance, tenderness of the abdomen, and painful micturition. It rarely happens that toxin sufficient to cause the death of the patient is generated, although there may be a certain amount of paralysis. In male children the penis is sometimes inoculated, but this is not serious. Diphtheria of the penis in adults is frequently mistaken for a chancre and has been followed by postdiphtheritic paralysis. Abner Post[1] reports the following case: H. entered the hospital four weeks after the beginning of his trouble. His brother-in-law, wife and child had all been ill with diphtheria and H. had cared for them. During the convalescence of the last one of the three, H. had a blister beneath the prepuce, which was followed by swelling and acute phimosis. An incision along the dorsum, made by his physician, was covered by a membrane. The entire prepuce finally sloughed. After his entrance to the hospital search for diphtheria bacilli was made in the discharge, but none were found. Ciliary paralysis in both eyes later developed and a postdiphtheritic paralysis in all four limbs. Nothing was found in the urine. Later, careful examination of the slough from the prepuce showed in places, a little below the surface, small clumps of bacilli which morphologically resembled diphtheria bacilli.

In a patient aged four years admitted to the South Department of the Boston City Hospital with scarlet fever, a short time after admission it was noticed that there was a profuse nasal discharge which irritated the upper lip. Cultures from this discharge showed diphtheria bacilli. Some weeks later there was pain and tenderness of the penis and some pain in micturition. Two days after, on retracting the foreskin, two small patches of membrane could be seen, the cultures from which were positive. These patches disappeared in a few days, leaving ulcerated spots that healed in a short time. This child had not been circumcised. The source of infection was, without doubt, the nasal discharge. Quite a number of similar cases have been observed at the South Department of the Boston City Hospital. Diphtheria of the penis is more frequent than is generally supposed. Some observers have reported diphtheria of the uterus during the puerperal stage.

[1] *Journal of Boston Society of Medical Sciences,* vol. ii, 1897.

Diphtheria of the eye, or diphtheritic conjunctivitis, is not infrequent. It is sometimes caused by the secretions from the throat of the patient being coughed into the eyes of the attendant, particularly in tracheotomy cases. The more common cause is auto-inoculation from the nasal discharge. Diphtheria of the eye commences with a slight congestion, which rapidly increases and is followed by the formation of a distinct membrane which has a grayish-white appearance, a little different from that of the membrane in the throat. The process goes on very rapidly, so that at the end of twenty-four or thirty-six hours the eye is so inflamed that it is impossible to separate the eyelids. There are two varieties of diphtheria of the eye—the superficial and the deep—each of which is very serious. In the former the eye is invariably lost; in the latter it is sometimes saved. There is a considerable amount of constitutional disturbance and usually severe pain. The rapidity with which the disease advances is very great, so that sometimes in forty-eight hours the eye is hopelessly destroyed. In the milder attacks, even when the eye is saved, the morbid process continues for six or seven days. If the attack comes on, as is not infrequent, during the course of measles, the probability of saving the eye is very slight. The general condition of the patient is also an important factor in the prognosis.

Diphtheria of the lungs. This is extremely rare but does occur. The focus is situated in one of the larger subdivisions of the bronchi, and the membrane rapidly extends to the bronchioles and to the larynx. The symptoms simulate those of pneumonia, and it is extremely difficult to make a differential diagnosis. The dyspnœa, however, is more marked than in pneumonia, and there is an absence of rusty sputum. The expectoration is mucopurulent, and cultures from it show the presence of diphtheria bacilli. It is reasonable to believe that primary diphtheria of the lungs is much more common than is generally supposed. The difficulty of making a correct diagnosis is sufficient to justify the conclusion that many patients die of what is called pneumonia who really have diphtheria of the lungs.

Complications.—In severe attacks an erythematous eruption may appear on various parts of the body, which must be distinguished from the eruption caused by antitoxin. This appears in severe attacks and is of grave import. Urticaria not connected with antitoxin sometimes appears but, although annoying, is not serious. Purpura hemorrhagica is present in the gravest types of the disease, and is generally the forerunner of death. Minute petechiæ appear on the body at first, and gradually increase in size until large spots of ecchymosis are present in the dependent portions. In some instances nearly the entire trunk may be the seat of this extravasion, only small areas of sound skin being apparent. Hemorrhage from the mucous surfaces is frequently present in severe types of the disease. There may be bleeding from the urethra and from the vagina. The hemorrhage, however, is more generally found to occur from the nose and mouth. The quantity of blood lost may be comparatively small, or so profuse as to endanger life.

Disease of the middle ear not infrequently occurs, and can be explained by the extension of the process through the Eustachian tube. Mastoiditis requiring operative interference is somewhat infrequent but the possibility of its occurrence should always be borne in mind

Nephritis is a constant symptom in the severer attacks and is also found in the milder forms. Its presence is explained by the action of the toxin on the kidneys. In the laboratory this has been demonstrated by autopsies on

guinea-pigs injected with diphtheria toxin, the kidneys being found in a state of cloudy swelling. The nephritis may be an early or a late symptom but generally occurs at the end of the second week. The presence of albumin in the urine was described fifty years ago by many observers, which ought to be a refutation of the statement that antitoxin causes albuminuria. The occurrence of albuminuria in diphtheria, as given by these early observers, varies from 70 to 55 per cent. Uræmia with marked convulsions appears in the graver types and there may be partial or complete suppression of urine. With complete suppression the condition, although very grave, is not necessarily fatal, for instances have been observed where no urine was passed for forty-eight hours and the patients recovered.

Cervical adenitis is frequent and in a certain proportion ends in suppuration. Cultures show the presence of streptococci and staphylococci. Abscesses elsewhere very rarely occur and, if at the site of injection, are generally due to some error in sterilization. In rare instances the serum may be at fault.

Bronchopneumonia appears during the second week in a large proportion of the cases, particularly of the laryngeal form, and is responsible for about 20 per cent. of the deaths in cases of intubation. Lobar pneumonia not infrequently commences during the second week but it is not nearly so frequent as bronchopneumonia, although a much more fatal complication.

Paralysis of a mild or severe type is one of the most frequent of the sequelæ and occurs in about 40 per cent. of all attacks of the disease. Some observers have given a much lower percentage, but this is due to the fact that the slight attacks of paralysis have not been recognized. The patellar reflexes are absent in a very large proportion of all cases, even when paralysis is not so marked as to attract attention.

Palatal paralysis characterized by a nasal voice is one of the most frequent forms. In some instances the uvula does not move during phonation and in others is deflected to one side. In the severer types of paralysis there is marked regurgitation of liquids, and sometimes an absolute inability to take any nourishment. Paralysis of the intrinsic and extrinsic muscles of the eye is common and is associated with double vision. The upper and lower extremities are sometimes paralyzed so that the patient is unable to move either his arms or his legs. Paralysis of the respiratory muscles sometimes occurs, and the patient has a peculiar shallow and sighing respiration. This has been observed in about 3 per cent. of the fatal cases at the South Department of the Boston City Hospital during the past nine years.

In a certain number of cases four or five weeks after the initial symptoms a multiple neuritis appears, with severe pain and loss of motion of the extremities. This condition is a very grave one and is a frequent cause of death.

The gravest sequel, and one that is responsible for the greatest number of deaths occurring in apparent convalescence is the effect of the toxin on the heart. In every case of diphtheria, mild or severe, the possibility of heart complications should always be in the mind of the physician, and frequent examinations of the heart should be the routine practice, no matter whether there are any symptoms referable to this organ or not. The heart complications are a phase of the degenerative changes in the nervous system, although in some of the fatal cases a degenerative change in the heart muscle has been found. Murmurs, usually systolic, are observed in the vast majority of patients with diphtheria. A rapid pulse rate is always cause for alarm and a slow pulse is an indication of serious trouble.

In the observation of the pulse rate of 800 cases of diphtheria the following results were reached: When the rate was less than 130, the mortality was 4.8 per cent.; when it was 130 the mortality was 16.2 per cent.; when 140 the mortality was 18.2 per cent.; when 150, the mortality was 40 per cent.; when 160, the mortality was 56.1 per cent.; when 170, there was a death-rate of 75 per cent.; and when the pulse rate was 180, the mortality was 90.9 per cent.

The conclusions reached by White and Smith[1] in the clinical study of 946 cases of diphtheria with reference to heart complications are of interest, the special points being:

1. "The great frequency of heart murmurs and irregularity of the pulse. The prognosis does not depend on the mere presence of these signs, but upon the severity of the infection, the length of time without treatment, the rate and degree of irregularity of the pulse, and the presence of the graver signs of cardiac disturbance.

2. "Moderate disturbance of the heart is very common; severe complications are infrequent.

3. "Frequent examinations of the heart are necessary to really determine its condition, because of the marked changes in rhythm from one hour to the next.

4. "Gallop rhythm, late vomiting, and epigastric pain and tenderness, are important as danger signals of severe heart complications. The association of late vomiting with gallop rhythm renders the outlook almost hopeless.

5. "Antitoxin does not affect the heart unfavorably, but, on the other hand, its early use prevents the appearance of grave heart complications.

6. "Frequent examination of the heart and pulse in the second and third weeks of the illness is necessary, that being the time when severe heart complications most frequently occur.

7. "Bronchopneumonia is a more frequent fatal complication of diphtheria than heart disease; sudden death from heart disease is very rare when patients are kept in bed for a proper period.

8. "Prolonged rest in bed is necessary in all severe cases; it is not necessary to keep all patients in bed who have cardiac murmurs and a pulse which is somewhat irregular and increased in rate. One should be governed by the stage of the illness and the general condition. If no serious heart trouble has developed within four weeks, the patients are usually safe from this complication.

9. "Heart murmurs and irregularity are of long duration in many cases and make it necessary to watch the condition of the heart long after convalescence in all severe cases."

Vomiting is, as a rule, an indication of commencing degeneration of the vagus nerve. There is no one symptom that should cause so much alarm in the convalescent stage of diphtheria as a sudden unexplained attack of vomiting. Very few patients in this condition recover. An example was seen in a patient admitted to the South Department of the Boston City Hospital in August, 1895. He had antitoxin, and everything progressed favorably until the 12th of September, when he complained of pain in the stomach and had a weak pulse. He passed a fairly comfortable night, but in the morning had persistent nausea and vomiting. He was restless, with a very rapid and

[1] *Medical Communications of Massachusetts Medical Society,* 1904.

feeble pulse; four hours afterward cyanosis appeared, the pulse became weaker, and he died about twenty-four hours after the commencement of the attack. This case was of particular interest because the patient was apparently convalescent and yet suddenly became collapsed and died in a short time. Acute endocarditis was found at autopsy. The pneumogastric nerve was examined by J. J. Thomas and showed marked degeneration of the nerve sheaths which in the fibers most affected were entirely replaced by drops of fat. In the fibers most affected no axis cylinders could be made out and the others showed in places swollen and beaded axis cylinders. The intensely degenerated fibers constituted approximately one-third of the nerve. This degeneration, although it has been carefully studied by some observers, does not seem to be sufficiently appreciated by the profession at large. The possibility of its occurrence during the convalescent stage of a comparatively mild attack cannot be too strongly emphasized.

Thomas,[1] from the study of 25 cases, describes the changes in the nervous system produced by diphtheria as: (1) a marked parenchymatous degeneration of the peripheral nerves, sometimes accompanied by an interstitial process, and hyperæmia and hemorrhages; (2) acute diffuse parenchymatous degenerations of the nerve fibers of the cord and brain; (3) no changes, or but slight ones, in the nerve cells; (4) acute parenchymatous and interstitial changes in the muscles, especially the heart muscle; (5) occasional hyperæmia, or infiltration, or hemorrhage in the brain or cord, in rare cases severe enough to produce permanent changes, such as the cases of multiple sclerosis and of hemiplegia which have been observed. It is probable that sudden death from heart failure is due to the effects of the toxic substances produced in the disease upon the nerve structures of the heart.

Diagnosis.—The diagnosis of pharyngeal diphtheria is based upon clinical appearances and upon the result of bacteriological examination of cultures taken from the affected parts. The temperature is not particularly elevated. In 1,000 consecutive non-fatal cases it was found that the maximum temperature in 4 instances was 105°, in 22 it was 104°, in 55 it was 103°, and in 919 it did not rise above 102° F.

The distribution of the membrane varies considerably. It may be confined to the uvula or one tonsil, or it may cover each tonsil, the uvula and the hard and soft palate, extending in some instances over the cheeks and to the lips. The tongue is sometimes, although rarely, invaded. In the fatal cases distinct membrane has been found in the antrum of Highmore.

The blood has been studied by many observers, but no very satisfactory results have been reached. Morse[2] says: "The examination of the blood in diphtheria is of no practical clinical importance in diagnosis, prognosis, or treatment. It affords no information which cannot be obtained more easily and more quickly in other ways."

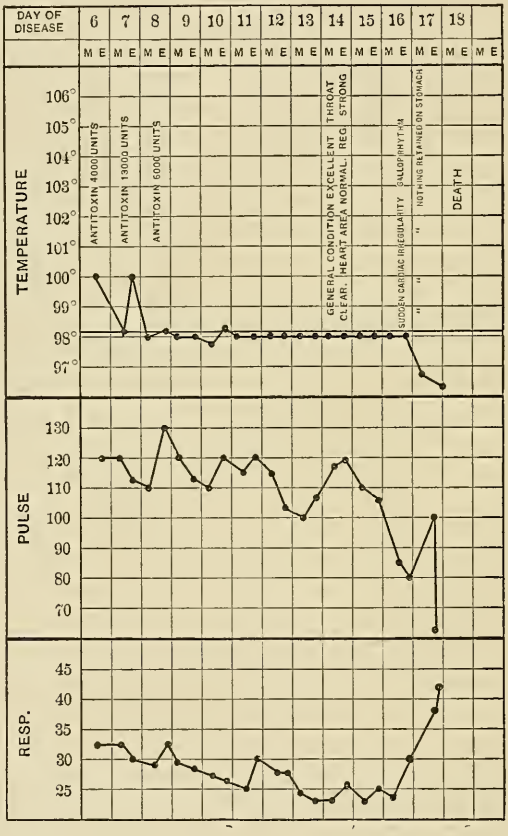
The temperature and pulse rate in a fatal attack, where there was very extensive membrane, sepsis, gallop rhythm, and nephritis, is of interest (Fig. 48). Fig. 49 gives the temperature and pulse in a moderately severe but non-fatal attack.

Tonsillitis is very frequently mistaken for diphtheria, and in many instances without the aid of cultures the error is unavoidable. The exudate on the tonsils in the early stage of scarlet fever is also frequently mistaken for

[1] *Medical and Surgical Reports, Boston City Hospital,* Ninth Series, 1898, page 83.
[2] *Boston City Hospital Reports,* Tenth Series.

diphtheritic membrane. These diseases are often associated, however, and a correct diagnosis is impossible without a bacteriological examination. An error in diagnosis is often made in syphilitic sore throats and in mercurial stomatitis. The laryngitis of a commencing attack of measles is often incorrectly diagnosed as laryngeal diphtheria. The appearance of the throat and the presence of Koplik's spots should prevent the occurrence of this error.

Fig. 48.


DAY OF DISEASE
6 7 8 9 10 11 12 13 14 15 16 17 18
M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE
106° 105° 104° 103° 102° 101° 100° 99° 98° 97°
ANTITOXIN 4000 UNITS
ANTITOXIN 13000 UNITS
ANTITOXIN 6000 UNITS
GENERAL CONDITION EXCELLENT THROAT CLEAR. HEART AREA NORMAL. REG. STRONG
SUDDEN CARDIAC IRREGULARITY GALLOP RHYTHM
" NOTHING RETAINED ON STOMACH
" "
DEATH
PULSE
130 120 110 100 90 80 70
RESP.
45 40 35 30 25

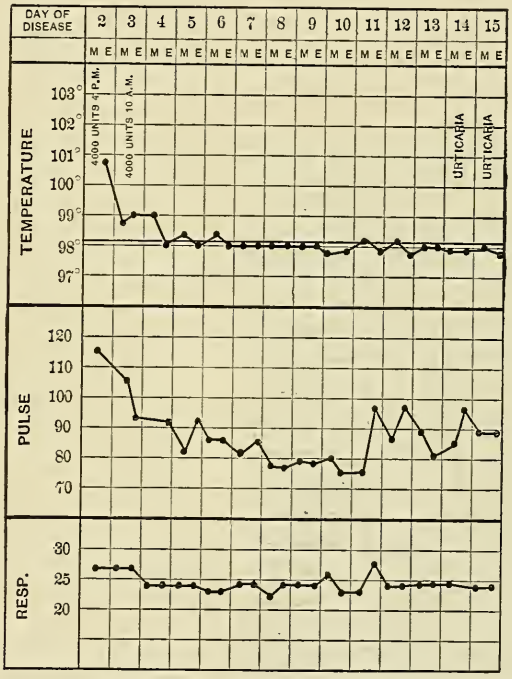
The temperature chart and pulse rate in a fatal attack of diphtheria.

Diphtheria may be present as a complication in any condition, but it more frequently occurs in measles than in any of the acute diseases, because the mucous membrane offers a fertile soil for the growth of the organism. Diphtheria also occurs with typhoid fever, with pneumonia, during the later stages of phthisis, and with scarlet fever. Much has been said regarding pseudodiphtheria, but the term is misleading, as the bacillus which is the cause of diphtheria is not found in the exudate.

The importance of a bacteriological examination in all cases of suspicious sore throat cannot be overestimated. Much has been said about the in-

accuracy of cultural diagnosis, and while mistakes may be made in the laboratory, the chances of error are very much less in cultural diagnosis than in the clinical. One great source of error is carelessness in taking the culture. The swab is simply put into the mouth and does not come in contact with the membrane. The swab should be rubbed near the edge of the diphtheritic membrane and not over the centre of the patch. Sometimes the swab is not rubbed sufficiently on the surface of the culture medium, and consequently there is no growth. These may seem trivial matters, but it is well before criticizing the work of the laboratory to be sure that the critic himself is not at fault. The reaction of the culture medium is sometimes the cause of a mistake, as the serum may be acid or very strongly alkaline. Sometimes the serum is perfectly dry, and when in this condition the growth is disappointing, as a certain amount of moisture is necessary. To sum up the whole matter

FIG. 49.



The temperature chart and pulse rate in a non-fatal attack of diphtheria.

in a few words: it can be said that, in a given case, if the culture medium is of the proper reaction, if there is a sufficient amount of moisture, if the culture is taken with care, and the tube placed in the thermostat within a short time after it has been inoculated, and allowed to remain there for at least eighteen hours, the results will be satisfactory. The examination of smears from an exudate in the throat are not very satisfactory. Many instances occur where a smear gives a negative result and a culture a positive one. It is therefore well not to place too much dependence upon an examination of a smear. If a culture is examined after it has been in the incubator

only six hours a positive report can be accepted, but a negative one should not be.

Some few years ago the writer made an examination of 500 throats in which the clinical diagnosis was doubtful but there was a suspicion of diphtheria. It was found that about 40 per cent. of the cultures contained diphtheria bacilli. A diagnosis of diphtheria in these cases would not have been possible without the aid of cultures. It was also noticed that, in many instances, a positive culture was obtained twenty-four or forty-eight hours before any membrane appeared. The most common organism found with the diphtheria bacillus was the *Staphylococcus pyogenes aureus*. The *Streptococcus pyogenes* was also found in a certain number of cases.

Allusion to the importance of taking cultures in nasal diphtheria has already been made, but it is well to strongly emphasize it again.

In laryngeal diphtheria cultures are frequently of no avail because the membrane is situated so far down that it is impossible to reach it with the swab, and, therefore, the diagnosis must be made from the clinical symptoms, namely, rigidity of the sterno-cleido-mastoid muscles, with supraclavicular and substernal retraction. If the patient is intubed, or if tracheotomy is done, cultures from the intubation tube or from the tracheotomy tube show the presence of the bacilli of diphtheria. In the vast majority of cases where there is substernal and supraclavicular retraction, dilatation of the *alæ nasi* and rigidity of the sterno-cleido-mastoid muscles, after excluding a retropharyngeal abscess, a peritonsillar abscess, and a foreign growth pressing on the larynx, the diagnosis of laryngeal diphtheria can confidently be made. In a patient admitted to the South Department of the Boston City Hospital, with the characteristic symptoms of laryngeal diphtheria, no membrane was seen in the throat and cultures were negative. He was immediately intubed. The intubation tube was rejected by coughing in about two minutes, and with it a cast of the larynx, trachea, and right and left primary bronchus (Fig. 50). Cultures from it gave an abundant growth of diphtheria bacilli. In an analysis of 1,500 intubations it has been found that positive cultures were obtained in only about 60 per cent.

Fig. 50.

Cast of the larynx, trachea and bronchi.

It must be conceded that there are chances of error in the cultural diagnosis, just as in every other department of medicine. The bacteriologist is no more likely to be infallible than the clinician. They must work together. Too much has been said about laboratory diphtheria and clinical diphtheria,

and the tendency has been to throw too much discredit upon the work of the bacteriologist. It is the duty of the physician to either examine cultures or have them examined in every case of suspicious sore throat, just as it is his duty to examine the urine in every case of acute disease.

An unnamed bacillus, the life-history of which has been studied by the writer, having a certain similarity to the bacillus of diphtheria, is not infrequently found in cultures from the nose. This organism is shorter and stouter than the bacillus of diphtheria; it is liquefying; it does not have the polar staining reaction; it does not stain by Gram; it is non-pathogenic for guinea-pigs; and when the growth is very abundant there is a distinct odor of old cheese. This organism is also found in cultures from the ear, particularly if there is a chronic discharge. This bacillus is very frequently mistaken for that of diphtheria.

Hofmann's bacillus morphologically very closely resembles that of diphtheria, but it is shorter and stouter. It does not react to the polar staining of Neisser. It is non-pathogenic for guinea-pigs. It has been claimed by certain observers that this organism was an attenuated form of the bacillus of diphtheria, and that under suitable conditions it may acquire virulence. This, however, has not been definitely proven, and in the light of our present knowledge must remain *sub judice*. The examination of cultures from the throat must always be made with great care, for other bacilli than the bacilli of diphtheria are frequently found, but a painstaking examination of the slide will reduce the chances of error to the minimum, and the probability of arriving at a correct diagnosis is much greater than when dependence is placed on the clinical appearances alone. It is very important that no antiseptic gargle should be used for at least two hours before the culture is taken. If this precaution is not observed there will be no growth on the serum, or the bacilli of diphtheria will grow so sparsely that they will be obscured by other organisms. Neglect to observe this precaution has frequently led to errors in cultural diagnosis.

The statement has been made that the bacillus of diphtheria is frequently found in cultures from the throats of healthy individuals who have not been exposed to diphtheria. Loeffler found this organism 4 times in the examination of cultures from 160 well children. Park and Beebe found it in 8 out of 330, and Kober 5 times in cultures from 600 individuals. Denny, of Brookline, Massachusetts, found the organism of diphtheria only once out of 235 cultures from normal throats.[1] The writer examined 130 throats with this point in view, and in no instance was an organism found that gave the same staining reaction as the bacillus of diphtheria. In a few instances bacilli were found having morphologically a marked resemblance to the organism of diphtheria, but the differentiation was easily made by the staining and cultural peculiarities.

The statement has been made that the bacillus of diphtheria is frequently found in the throats of perfectly well persons who have the care of patients ill with diphtheria The writer's experience is the opposite of this. In order to show that the organism is not found, as a rule, in the throats of attendants of patients ill with diphtheria, cultures were taken from the throats of sixty nurses on duty in the diphtheria wards of the South Department of the Boston City Hospital, and in no instance was the bacillus of diphtheria found.

[1] *Bacteriology and the Public Health,* George Newman, M.D.

Previous to the discovery of the bacillus the question of the release from isolation of a diphtheria patient was a very difficult one to decide. By cultural examination the physician is now able with certainty to say that the patient is free from infection. Two negative cultures from the throat and nose should always be required. In certain rare instances the bacillus may remain in the throat for a very long time, but in these the organism, as a rule, is non-virulent and the inoculation of guinea-pigs will definitely settle the question of virulence. As a matter of fact a cultural examination shortens rather than lengthens the period of isolation. Goodall, Medical Superintendent of the Eastern Hospital, London, states,[1] for the year 1903, that "no diphtheria patient has been discharged from the hospital until two consecutive bacteriological examinations of the fauces have proved negative. It was expected that, in consequence of this, the period of detention would be lengthened; but, as a matter of fact, it was shorter than in any year since 1899, when it was 57.6 days. As in that year no bacteriological examinations for discharge were made, all one can say at present is that these examinations do not appear to lengthen the period of detention of diphtheria patients in hospital. Whether the incidence of 'return cases' is lessened is a matter of inquiry." So far as "return cases" of diphtheria are concerned, it may be said that they are of such rare occurrence at the South Department of the Boston City Hospital as to prove the very great importance of cultures for discharge, as in no other way can it be definitely shown that the individual is free from infection. Cultures for discharge should be commenced seven days after the disappearance of the membrane and the cessation of the discharge from the nose. It is a waste of time and labor to take cultures any earlier, and if the condition of the patient is satisfactory it is unnecessary to wait any longer.

In the larger cities, Boards of Health have established laboratories for examining cultures. In the country the physician must depend upon himself. The apparatus required is a microscope with an oil immersion lens, an incubator and culture tubes. The best culture medium is Loeffler's blood serum, but, as it is difficult to obtain the blood, egg albumin or agar agar with Loeffler's bouillon can be substituted. The egg albumin is solidified in a coagulator, and then sterilized in the usual way. When it is necessary to have an immediate culture, an egg can be boiled for four minutes and the shell chipped off. The egg is then placed in a deep glass and the ordinary cotton plug is inserted. The exposed surface of the egg can be inoculated with the ordinary swab and placed in the incubator Satisfactory results can be obtained in this way, although it is a somewhat cumbersome method.

Prognosis.—The prognosis in every case should be guarded. It depends upon the location and extent of the membrane and upon the later symptoms. The temperature is of no assistance in the majority of instances in making a prognosis. An extensive and rapid formation of membrane is always a sufficient cause for an unfavorable prognosis. Age is an important factor in deciding the result in a given case. The two extremes—infancy and old age—should always be taken into consideration, as the death-rate at these periods is always high. The rapid disappearance of the membrane is a good indication; its persistence an unfavorable one. Necrosis of the mucous membrane near the site of the exudate is a very grave symptom.

[1] *Annual Report of the Metropolitan Asylums Board.*

A profuse discharge from the nose is sufficient reason to fear a fatal termination. Delirium, whether violent or of the low muttering type, is of the gravest import. Hemorrhage from the mucous surfaces, if profuse, is generally followed by death. Spots of ecchymosis appearing as minute points and rapidly extending are the forerunners of death. A rapid pulse with gallop-rhythm and a very slow pulse with feeble heart sounds render a fatal termination certain. Vomiting at the outset of the attack is not a serious symptom but nausea and vomiting late in the course or during apparent convalescence are always an indication of a very serious condition. It may be emphatically stated that an unexplained attack of vomiting during the convalescent stage is sufficient cause for an unfavorable prognosis. Cervical adenitis, whether occurring early or late, is not particularly unfavorable. If suppuration takes place, although convalescence may be prolonged, unless there is very deep and extensive burrowing of pus, which is rare, the life of the patient is not in jeopardy.

Pneumonia and bronchopneumonia are always grave complications. The prognosis must depend upon the extent of lung tissue involved, with the qualification that any inflammatory process occurring in the lung in the course of diphtheria is much more serious than when it occurs in other diseases or idiopathically.

Nephritis, if severe, must always be considered a serious indication, and daily examinations of the urine should be made, not only to detect the presence of albumin and casts, but also to determine the quantity of urea eliminated. There is always a certain amount of albuminuria in diphtheria, but death from this cause is not of very frequent occurrence.

Paralysis should always cause apprehension—depending on its extent. Palatal paralysis may interfere with deglutition to such an extent as to prevent the ingestion of sufficient food and expose the patient to the danger of an inhalation pneumonia. Heart complications are always a cause for anxiety. The significance of gallop-rhythm, so far as a fatal issue is concerned, cannot be too strongly emphasized. A sudden slowing of the pulse rate is an indication of the failure of the heart's action and consequent death. Empyema, although it rarely occurs, is a sufficient reason for an unfavorable prognosis.

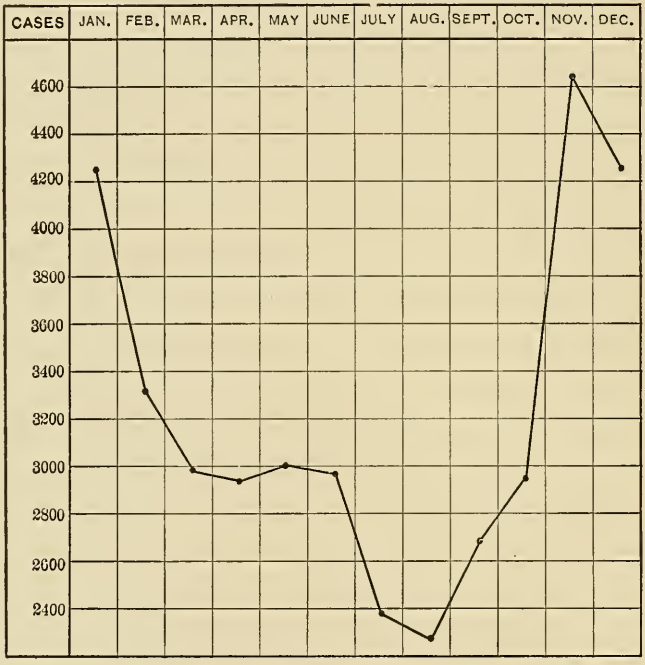
In laryngeal diphtheria, after the stenosis has been relieved by operative interference, the possibility of bronchopneumonia should always be considered, and if it occurs the prognosis is always unfavorable. If the membrane is extensive, even if it has exfoliated, recovery should be considered doubtful. Septic infection is always a serious complication, and is frequently the most important factor in causing death in the early stages. The average death-rate in this country varied from 30 to 50 per cent. previous to the introduction of antitoxin. When an outbreak appeared in rural districts, the mortality rate was always very high. Bayeux gives the mortality rate of diphtheria previous to the introduction of antitoxin as 55 per cent.

Prophylaxis.—As diphtheria is an infectious disease, in order to diminish its prevalence, it is important that infected individuals should be isolated. The room should be stripped of all hangings. The carpet and all furniture not absolutely required should be removed. Although the danger of the germs being carried by *fomites* is not so great as in some other infectious diseases, these precautions should always be taken, for the smaller the number of things to be disinfected, the less the danger of inefficient disinfection.

The area of infection of diphtheria is comparatively small, and therefore a patient can with care be sufficiently isolated in a house occupied by one family The great danger of infection arises not from the patients who are seriously ill, but from the mild and unrecognized attacks of the disease, principally of the nasal type.

The effect of these mild cases in increasing the prevalence of diphtheria, particularly in the public schools where children are brought in close contact, is manifest (Fig. 51). It will be seen that during the months of July and August, when the schools were not in session, the number of cases reported

Fig. 51.



Cases of diphtheria in Boston, Mass., by months, reported to the Board of Health from 1890 to 1904, inclusive.

was very considerably less than during term time. It is noticeable that the falling off in the number from June to July is very marked, and it is also a significant fact that the increase commences in September as soon as the schools are open; and also that the increase from October to November is very marked. It has been claimed that this increase from September was due to meteorological conditions, but this is not tenable, because in September, October, and November the climatic influences are not sufficient to explain the prevalence of the disease, any more than they would explain the diminution in the number of cases during February and March. The obvious conclusion is that there should be a careful medical inspection of schools in order that all children with mild attacks of diphtheria should be excluded, which would be a very important factor in diminishing the prevalence.

Disinfection of the clothing and bed-linen is important, and, although this can be done with corrosive sublimate and boiling at the home of the patient, it could be much more satisfactorily performed if municipalities would establish sanitary wash-houses and disinfecting stations to which the infected articles could be sent. Much has been accomplished in this way by the sanitary wash-house established in Glasgow a few years ago. Disinfection of the room after recovery is a difficult problem, particularly in a tenement house. Most of the disinfection as now done is not effectual. If possible the ceiling, walls, and floor of an infected room should be washed with corrosive sublimate. If the walls are papered, they can be rubbed with bread, the soft part of the bread acting like the bristles of a brush and the crust as the handle. It is preferable, however, to remove the paper and repaper and repaint the room. Formaldehyde in a gaseous form, if generated in sufficient quantity and if the room is tightly sealed by means of paper pasted around the window-frames and door-casings, is an effectual mode of disinfection. If there is any clothing in the room to be disinfected by formaldehyde, it must be loosely hung on the backs of chairs or on suitable racks. Formaldehyde has no penetrating power. As illustrating this fact, the writer made the following experiments: Cultures from diphtheria patients, cultures of the typhoid bacillus, and cultures of the pus cocci, were placed on pieces of cloth and at the same time similar cultures were placed in the pockets of coats. The room was tightly sealed and the formaldehyde was generated by a Trillat's autoclave. It was found that, while the cultures exposed directly for twenty hours to the gas were sterile, those placed in the pockets of the coats showed abundant growths of the different organisms. Harrington[1] arrived at similar results in his experiments. The conclusion reached by the majority of investigators is that formaldehyde is a most powerful and practical disinfectant for large air spaces, but that it has no penetrating power. It is important that a sufficient amount of the gas should be generated, and it is equally important that the room should be very tightly sealed. The neglect of carefully doing this is responsible for the failure in this method of disinfection. The statement has been made that formaldehyde is not dangerous to animal life. A more incorrect observation could not be made. If sufficient formaldehyde is generated to destroy the microörganisms of disease, it must necessarily destroy animal life. In a series of experiments by the writer, rabbits were placed in a room that was to be disinfected by this method and died in from two to three hours.

There are many different apparatuses for generating formaldehyde; some are expensive, others quite cheap; some are effectual and others are useless. The Trillat autoclave is a very good apparatus. Lentz's generator is very useful. Schering's paraform lamp is perhaps as good an apparatus as can be used. The simplest, and also an effectual, method of generating formaldehyde is that adopted by the Maine Board of Health, which consists of mixing potassium permanganate with a 40 per cent. solution of formalin. The potassium permanganate should be the commercial and not the chemically pure. No special apparatus is required. An ordinary tin dish with flaring sides can be used. The quantity of permanganate for each pint of formalin is six and one-half ounces. It is very important that the permanganate be put into the dish first, and then the formalin solution poured over it. It is

[1] *Practical Hygiene*, by Charles Harrington, M. D., 1905.

taken for granted that the room has been tightly sealed. As soon as the formalin is placed in the receptacle, a rapid exit must be made, because the gas is generated very quickly. The room should remain closed for twenty-four hours and then be thoroughly aired. The quantity of the 40 per cent. solution of formalin and of the potassium permanganate to disinfect 500 cubic feet of space is one pint of the former and six and one-half ounces of the latter.

Steam under pressure is the best method of disinfecting mattresses and woolen material. In many of the large cities, both in this country and in Europe, steam disinfecting plants have been established. In some parts of Europe a square chamber is used. In this country a cylinder is the favorite mode of construction. The advantage of the latter shape is that a cylinder that will stand a pressure of fifteen pounds to the square inch can be more easily constructed than a square or oblong chamber. A portable steam disinfector which weighs about the same as a steam fire-engine has been devised. This apparatus, although not suitable for cities, can be used to great advantage in sparsely settled districts, and could be owned and operated by three or four adjoining towns.

The disinfection of upholstered furniture is a difficult problem. Immersion in boiling naphtha is a satisfactory method. As the boiling point of naphtha is about 140°, a temperature sufficient to kill nearly all bacteria after an exposure of two hours, and as the melting point of glue is 212°, it is evident that the glued parts of the furniture would not be injured. A few experiments have demonstrated the truth of the foregoing statement. So far as is known, this process has not been adopted in this country to any extent.

Sunlight is one of the most efficient disinfectants. Experiments have shown conclusively that many of the pathogenic microörganisms are destroyed by exposure to the direct rays of the sun for two or three days. It is, therefore, evident that in the country, where the necessary apparatus for disinfection is not obtainable, much can be accomplished by the direct exposure of the clothing of the patient to sunlight. Disinfection can never take the place of cleanliness, fresh air, and sunlight, although this fact is not fully appreciated by the general public.

Domestic animals may be sources of infection. Cats and dogs may contract diphtheria from a child ill with this disease, and in turn communicate it to other children. Several instances have occurred where cultures from cats and dogs showed the presence of the bacilli of diphtheria, and it was definitely proved that these animals had communicated the disease to human beings. The conclusion is obvious,—that cats and dogs should always be excluded from the room where a patient is ill with diphtheria. The role that domestic animals play in the propagation of contagious disease has not been sufficiently appreciated by Boards of Health in this country.

Personal Prophylaxis.—A few words regarding personal prophylaxis may not be inadmissible. The physician and nurse who have charge of diphtheria patients should be careful regarding the patient coughing into their faces. In tracheotomy cases, while dressing the wound, or cleaning the tube, it is well to wear glasses. All abrasions on the hands should be carefully protected. Cloths used for handkerchiefs should be immediately burned or placed in a sterilizing solution. It is not advisable to wear a gauze muzzle, because the area of infection of diphtheria is slight, the medium of communication being the discharge from the nose and mouth.

The writer made an investigation on this point and found that the dust in diphtheria wards did not contain diphtheria bacilli. Cultures were taken from the ledges of windows, the ventilators and the floors, and in no instance were diphtheria bacilli found. To demonstrate that diphtheria is not an air-borne disease, flasks of bouillon through which the air of the diphtheria wards was pumped for an hour were used. It was found that, although the bouillon after having been in the incubator for twenty-four hours showed an abundant growth of different organisms, principally the *Bacillus subtilis* and cocci, no diphtheria bacilli were detected. Flies are not the carriers of infection, as has been demonstrated by experiments by the writer of which it is unnecessary to give a detailed account; but they were sufficient to demonstrate the truth of the foregoing statement.

Susceptibility.—The subject of susceptibility is germane to that of prophylaxis. The young are particularly susceptible. The statement has been made that nursing infants very rarely contract this disease but such is not the case. If a nursing child is brought into immediate contact with an individual ill with diphtheria, there is very strong probability that he will contract the disease. The comparative immunity of nursing infants is due not to lack of susceptibility, but to the fact that they are more carefully protected and less likely to be exposed. Advanced age does not necessarily give immunity. The comparatively small number of elderly individuals attacked with diphtheria is explained by the fact that at this epoch of life more care is exercised in the indiscriminate use of handkerchiefs and in promiscuous kissing. Kissing, and the transfer of chewing gum from one individual to another, have been the cause of outbreaks of diphtheria in several instances.

Adenoids and hypertrophied tonsils increase the susceptibility of the individual, and when these conditions obtain the importance of operative interference is evident. An individual who is subject to repeated attacks of tonsillitis is particularly susceptible to diphtheria. The general condition has no influence on susceptibility: the most robust are just as likely to contract the disease as the most delicate. At the South Department during the past nine years, of the 460 nurses on duty in the diphtheria wards, 30 per cent. contracted the disease. As these women were supposed to be in good health, it is evident that the statement just made regarding susceptibility of robust individuals is founded on fact and not on theory.

Treatment.—**General.**—Attention should be given to the hygienic surroundings, and fresh air and sunlight are important aids. Allusion has already been made to the importance of isolation. The physician in making his visits should wear a gown, and should be careful to wash his hands in a solution of corrosive sublimate after having seen the patient.

The diet during the acute stage should be liquid—milk and broths. Milk, however, is the most satisfactory and should be given in sufficient quantities at least every four hours, and oftener if desired. If there is nausea, peptonized milk or lime water and milk can be used. If no food can be retained, rectal enemata consisting of milk and egg can be used. Feeding every fifteen minutes is always to be avoided in diphtheria. The patient must not be annoyed by injudicious attempts to induce him to take food and stimulants at short intervals. Overzealousness in this particular has undoubtedly caused many deaths. Ice-cream is frequently very grateful and can be given in unlimited quantities. Alcohol in the severer cases is of much benefit, and

whisky or brandy can be given in as large doses as the stomach will bear. It is impossible to state definitely the quantity that should be given at each dose. A moderate dose may be administered at first, and gradually increased according to the condition of the stomach. It is surprising the amount of alcohol that a patient ill with septic diphtheria will take with positive benefit. Champagne, as a rule, is not well borne but in exceptional cases may be given with benefit. Digitalis in doses proportioned to the age is sometimes of benefit at the commencement, but in the later stages is much more likely to do harm than good, particularly when there is beginning degeneration of the heart muscle or cardiac nerves. The bowels should be kept open by mild cathartics, and the best agent is calomel in small and frequently repeated doses. Diuretics, if there is albuminuria, are to be avoided, but it is well to give a considerable quantity of water if there is no nausea. Corrosive sublimate in very small doses sometimes is of benefit, but it should be given with the utmost care. It is well to commence with $\frac{1}{60}$ of a grain for a child five years old and proportionate doses for younger children. Jacobi speaks very highly of this mode of treatment, and it certainly is of advantage in some cases. Antipyretics should not be given, for not only are they injurious to the patient, but there is no special reason for their use, as the temperature in diphtheria, except in rare instances, is not specially elevated. Pilocarpine is inadmissable on account of its debilitating effects. Tincture of chloride of iron is advised but the advantage derived from its use is problematical. Sometimes, when the patient is violently delirious, a small dose of morphia may have a quieting effect, but this drug should always be given with the utmost caution. Strychnia is a most useful stimulant and can be administered to very young children in proper doses with great advantage. When there is a collection of mucus in the intubation tube, atropine can be given with seeming benefit, but a second dose should not be given until the effect of the first has passed off. In collapse, nitroglycerine will frequently be of use for a time, but its effect is transient. For a better understanding of the doses of the four drugs just mentioned, the following table taken from *Rotch's Pediatrics* is appended:

Age.	Tincture Digitalis.	Strychnine.	Nitroglycerine 1 per cent. solution.	Atropine.
	Minim.	*Grain.*	*Minim.*	*Grain*
3 months	$\frac{1}{10}$ to $\frac{1}{2}$	$\frac{1}{2000}$ to $\frac{1}{1000}$	$\frac{1}{75}$ to $\frac{1}{50}$	$\frac{1}{3000}$ to $\frac{1}{1500}$
6 months	$\frac{1}{10}$ to $\frac{3}{4}$	$\frac{1}{1500}$ to $\frac{1}{500}$	$\frac{1}{25}$ to $\frac{1}{15}$	$\frac{1}{2500}$ to $\frac{1}{1000}$
9 months	$\frac{1}{4}$ to 1	$\frac{1}{1000}$ to $\frac{1}{300}$	$\frac{1}{25}$ to $\frac{1}{10}$	$\frac{1}{1500}$ to $\frac{1}{750}$
12 months	$\frac{1}{4}$ to $1\frac{1}{2}$	$\frac{1}{500}$ to $\frac{1}{250}$	$\frac{1}{25}$ to $\frac{1}{5}$	$\frac{1}{1000}$ to $\frac{1}{500}$
2 years	$\frac{1}{2}$ to 2	$\frac{1}{500}$ to $\frac{1}{150}$	$\frac{1}{15}$ to $\frac{1}{3}$	$\frac{1}{750}$ to $\frac{1}{250}$
3 years	$\frac{1}{2}$ to 3	$\frac{1}{300}$ to $\frac{1}{100}$	$\frac{1}{10}$ to $\frac{1}{2}$	$\frac{1}{500}$ to $\frac{1}{200}$
4 to 10 years	1 to 5	$\frac{1}{200}$ to $\frac{1}{60}$	$\frac{1}{2}$ to $\frac{3}{4}$	$\frac{1}{250}$ to $\frac{1}{150}$
10 to 12 years	3 to 8	$\frac{1}{100}$ to $\frac{1}{40}$	$\frac{1}{2}$ to 1	$\frac{1}{200}$ to $\frac{1}{100}$

It is well to bear in mind that diphtheria is a debilitating disease, and therefore food and stimulants that can be the most easily assimilated should be given.

In septic cases with marked failure of the action of the heart the injection of a pint of normal salt solution is frequently of great use. The writer has seen instances of recovery of apparently moribund patients after this treatment. It is important that the patient should remain in bed for a considerable time, even after apparent convalescence is established.

Local Treatment.—In studying the history of diphtheria one can not help being impressed with the number of different remedies that have been used for the removal of the membrane. Many of these have done more harm than good. Any local application that causes pain to the patient is positively harmful. All that can be done is to cleanse the mouth in the easiest way possible without exhausting the strength of the child. Loeffler's solution (menthol, 10 grams, dissolved in toluol to 36 cc., liq. ferri sesquichlorati 4 cc., and absolute alcohol 60 cc.) is a very good application. It can be used with a swab of absorbent cotton, and does not cause irritation. Irrigation with corrosive sublimate 1 to 2,000 is often of use. Boracic acid irrigation frequently gives relief; irrigation with normal salt solution cleanses the mouth and removes all detached pieces of membrane. Irrigation is done by turning the child on the side and introducing the nozzle of a fountain syringe, the force of the stream being regulated by the elevation of the bag. Children will not use gargles and are frightened by sprays, but very soon become accustomed to irrigation and submit to it without struggling. Peroxide of hydrogen has been used to a very great extent. It is doubtful how much good has been accomplished by it. Papayotin in 5 per cent. solution has been used as a direct application with a sponge or brush. Lactic acid has been used for removing the membrane and certainly does no harm, but the amount of good that it accomplishes is doubtful. Dobell's solution either as a spray or as a gargle sometimes seems to be of benefit. If dysphagia is marked, painting the fauces with a 1 to 2 per cent. solution of cocaine will frequently give relief, but it has no effect on the diphtheritic membrane. When there is profuse discharge from the nose the nostrils should be thoroughly cleansed with a swab wet with some mild antiseptic solution, and then calomel insufflated. The nasal douche is to be avoided on account of the danger of its causing middle ear disease. A few years ago it was the writer's practice to use the nasal douche in all cases where there was a profuse discharge from the nose, but this treatment increased the number of cases of trouble in the middle ear. It has, therefore, been discontinued, with the result that otitis media has been very much less frequent.

Cervical adenitis is very frequently relieved by the application of ice. Sometimes, particularly with children, warm applications, such as corrosive sublimate or creoline poultices, are more grateful. If suppuration takes place, early incision is imperative. In rare instances pus may burrow under the deep cervical fascia and deep incisions may be required but this is the exception. A bulging of the membrana tympani demands paracentesis. This condition occurs in about 4 per cent. of all cases. A mastoiditis characterized by a rise in temperature, œdema, and tenderness behind the ear, requires prompt operative interference. Because the patient is ill with diphtheria, there is no reason why the operation should be postponed.

Inflammation of the mastoid cells is of rare occurrence, but the probability of this complication must be borne in mind.

The treatment of postdiphtheritic paralysis must be expectant. Electricity does not do any good. Strychnia and iron as general tonics are useful, but the important things in the treatment of this sequel are rest in bed and nourishing diet. If the palatal paralysis is so marked as to interfere to any great extent with deglutition, resort must be had to œsophageal feeding.

Serumtherapy.—Behring, Roux, Martin, Chaillou, and Yersin experimented for a long time before arriving at definite conclusions regarding the effectivity of the serum of animals rendered immune to diphtheria by constantly increasing doses of the toxin, in the treatment of this disease. In the latter part of 1890 Behring made the statement that the serum of animals immune to diphtheria was an important remedial agent in the treatment of the disease. The first use of the serum on man was not particularly successful because the antitoxin was not of sufficient strength. Later, however, Behring, Ehrlich, Roux, and Martin, increased the strength of the serum and had gratifying results. The most comprehensive account of the investigations on antitoxin was given by M. Roux at the International Congress of Hygiene and Demography at Budapest in 1894. The statistics that he gave were remarkable. He stated that in certain hospitals where the death-rate from diphtheria had been 58 per cent. before antitoxin was known, since its advent the rate had fallen to 20 per cent. It is a matter of common experience that, previous to 1894, every physician in the country who had to deal with diphtheria felt that he had a hopeless problem to solve, and therefore the reports that came from the other side of the water of the beneficial results of the serum treatment were received with scepticism at first, then with partial belief, and, later, when it was fully demonstrated that antitoxin was instrumental in decreasing the death-rate, with full belief in its efficacy.

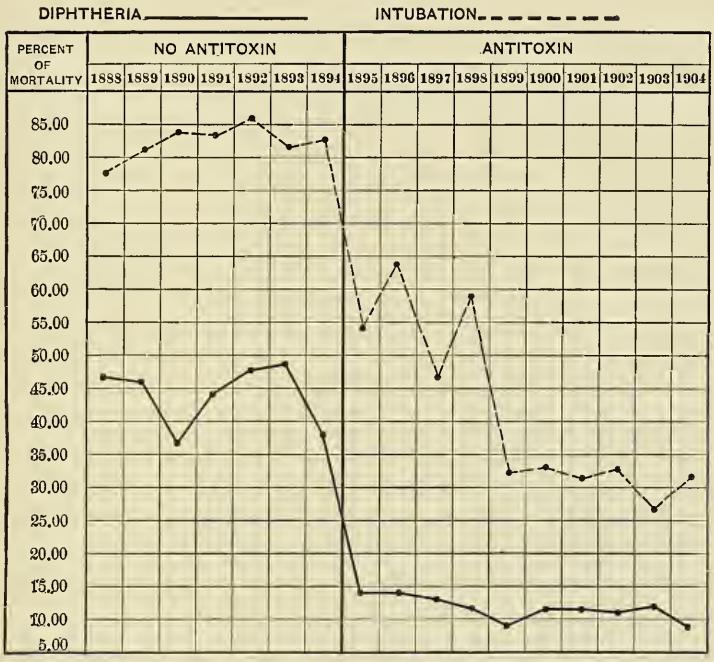
Bayeux, in his monograph on diphtheria, makes the statement, based upon an analysis of 230,000 cases reported from all parts of the world, that the death-rate of diphtheria before antitoxin was used was 55 per cent. and that since the advent of the serum it has fallen to 16 per cent.

Boston, Massachusetts, has suffered more from diphtheria than any of the larger cities in this country. Why diphtheria has been more prevalent in Boston than in any other city has not been satisfactorily explained. The death-rate at the Boston City Hospital, proper, before antitoxin was used, from 1888 to 1894, was 43.20 per cent. The death-rate from 1895, in the latter part of which year the South Department was opened and antitoxin given to every patient ill with diphtheria, to 1904, inclusive, was 11.84 per cent.

Fig. 52 shows the per cent. of mortality of diphtheria at the Boston City Hospital, proper, and at the South Department from 1888 to 1904, inclusive, with the per cent. of mortality of intubations for the same time. By following the full black line it will be seen that previous to 1895 the death-rate varied from 46 per cent. in 1888 to 48 per cent. in 1893. In 1890 and in 1894 the death-rate was 36 and 38 per cent., respectively. In 1895, in the latter part of which year the South Department was opened, the death-rate fell to 14 per cent. In the earlier part of 1895 antitoxin was given to a certain extent and there was a marked diminution in the death-rate. In 1896 the death-rate was 14 per cent., and since that time it has diminished gradually to 9.5 per cent. This diminution from 14 per cent. may be explained by the

administration of large doses of antitoxin to patients already apparently moribund and also by the fact that patients are now admitted to the hospital earlier in the course of the disease than during 1895 and 1896. It has been stated that the death-rate in 1904 was 9.5 per cent., but it is of interest to note that if the deaths that occurred within twenty-four hours of admission are eliminated, of which there were forty, the actual mortality of diphtheria amenable to treatment is found to be for the year 6.95 per cent. In Fig. 52 the broken line

Fig. 52.



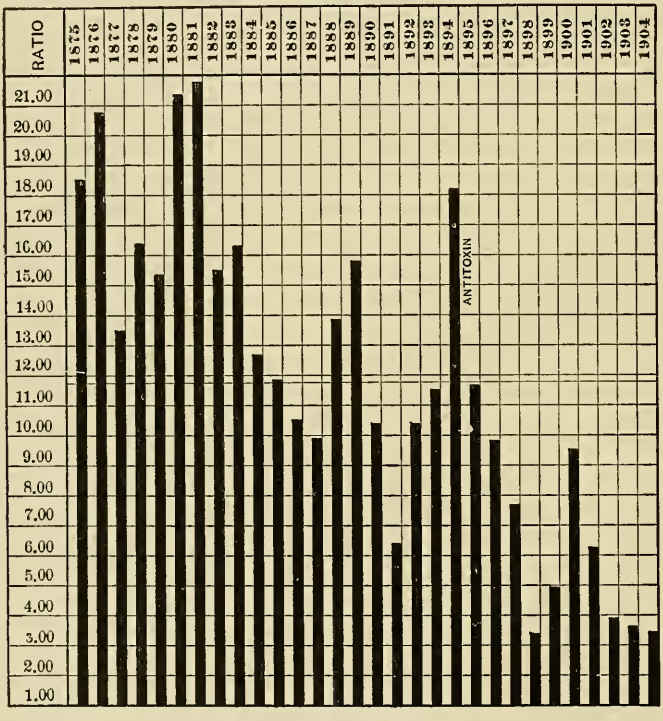
Per cent. of mortality of diphtheria at the Boston City Hospital, proper, and at the South Department from 1888 to 1904, inclusive. Per cent. of mortality of intubations for the same time. 1888 to 1894 no antitoxin. 1895 to 1904 antitoxin.

represents the mortality percentage of intubation cases, and it will be found by looking at the chart that the mortality rate of intubation cases previous to the use of antitoxin varied from 78 to 86 per cent. On the other hand, from 1895 to 1904, the mortality rate of operative cases of laryngeal diphtheria varied from 64 to 26 per cent. Since 1899 the death-rate in the operative cases at the South Department has varied from 33 to 26 per cent. In 1903 the death-rate was 26.61 per cent. and in 1904 it was 30 and a large fraction. To state these facts more succinctly: in the seven years at the Boston City Hospital, proper, from 1888 to 1894, inclusive, more than three-fourths of patients with laryngeal diphtheria requiring operative interference died, while from 1895 to 1904, particularly since 1900, nearly three-fourths recovered. This diminution in the mortality rate can only be explained by the use of antitoxin. In the annual report of the Metropolitan Asylums Board of London for 1903, it is stated that at the eleven hospitals

under the jurisdiction of this Board, where 4,839 patients were treated with antitoxin, the death-rate from diphtheria was 10.18 per cent. If in the same hospitals the death-rate from the tracheotomy cases for 1903, which was 31.82, is compared with the death-rate of the intubation cases at the South Department for the same year, which was 26.61, it will be seen that there is a diminution of 5 per cent. in the intubation cases at the South Department as compared with the tracheotomy cases at the London hospitals. In the London hospitals there were 176 tracheotomies and at the South Department were 139 intubations during the year.

The effect of antitoxin and hospital treatment on the death-rate of Boston is shown by Fig. 53, which indicates the ratio of mortality of diphtheria per

FIG. 53.



Ratio of mortality of diphtheria per 10,000 of the population in Boston, from 1875 to 1904, inclusive.

10,000 of the population for thirty years, from 1875 to 1904, inclusive. It will be seen that for the twenty years from 1875 to 1894 before antitoxin was used, the rates of mortality ranged from 21.78 to 6.23, with an average for this time of 14.46 per 10,000 of the population. If a comparison is made for these twenty years with the nine years commencing with 1896 and ending with 1904, it will be seen that in only one year of the twenty was the death-rate as low as it has been from 1896 to 1904, inclusive. The year 1895 is purposely omitted because the South Department was not in operation until August 31st of that year Since 1896, when the ratio of mortality was 9.80 per 10,000 of the population, it has gradually fallen, with the exception

of one year when it was 9.57, an epidemic year, to 3.35 per 10,000 of the population, the rate for 1904. This reduction in the mortality rate is the legitimate result of the general administration of antitoxin and hospital treatment. For the twenty years from 1875 to 1894, the average ratio of mortality per 10,000 of the population in Boston was 14.46, while that from 1895 to 1904, inclusive, was 6.42,—a diminution of more than one-half.

In order to derive the greatest possible advantage from antitoxin it should be given at the earliest possible moment in the course of the disease, even before the membrane has commenced to form. It is at this time, when there is a certain amount of congestion of the mucous membrane of the throat that a bacteriological examination is of great use, because almost invariably at this stage a positive culture will be obtained. If antitoxin is given at once, it will prevent the formation of membrane. This has been proved by numerous experiments in the laboratory. It has also been demonstrated by experience.

Unfortunately the physician, as a rule, is not called until there is a certain amount of membrane in the throat, and much valuable time is lost. In the report of the State Board of Health of Massachusetts for 1902 is an interesting table giving the fatality per cent. of diphtheria according to the day of the administration of antitoxin. In 1,433 cases in which antitoxin was given on the first day the mortality was 7.9 per cent.; when the serum was given on the second day in 3,284 cases, the percentage was 6.2; when it was given on the third day in 2,654 cases, the percentage was 9; on the fourth day in 1,687 cases, the percentage was 12.9; on the fifth day in 864 cases, the rate was 15.9 per cent.; on the sixth day and later in 1,242 cases, the percentage was 17.6. It must be taken for granted that, when it was stated that antitoxin was given on the first day of the disease, the chances are that, in many instances, the physician did not see the patient until the second day, when the symptoms were pronounced; but even with this source of error, the importance of the early administration of the serum is demonstrated. At the South Department there have been 190 cases of diphtheria among the doctors, nurses, and employees since September 1, 1895, and *there has not been a death*, which is due unquestionably to the fact that antitoxin was administered in large doses at the outset of the attacks even in many instances before there was any membrane apparent, but where the mucous membrane of the throat presented the peculiar congested appearance which is characteristic of the first stage of the disease.

MacCombie, in the Annual Report of the Metropolitan Asylums Board, London, for 1893, gives some interesting figures illustrating the advantages of the early administration of antitoxin. He says that from 1897 to 1903, inclusive, of 187 cases treated on the first day of the disease the percentage of mortality was 0. Of 1,186 cases treated on the second day of the disease the mortality for 1897 was 5.4 per cent.; for 1898, 5; for 1899, 3.8; for 1900, 3.6; for 1901, 4.1; for 1902, 4.6; for 1903, 4.2. Of 1,233 cases treated on the third day for the corresponding years the percentages were 11.5, 14.3, 12.2, 6.7, 11.9, 10.5, 17.6. Of 963 cases treated on the fourth day for the same years the percentages were 19, 18.1, 20, 14.9, 12.4, 19.8, 16.7. Of 1,260 cases treated on the fifth day and after, the percentages are 21, 22.5, 20.4, 21.2, 16.6, 19.4, 17.3. It is an interesting fact that the mortality, when treatment was delayed to the fifth day and afterward is four times, and in some cases five times, as great as when antitoxin was given on the

second day of the disease. The statement has been made by certain observers that antitoxin is not effectual after the fourth or fifth day of the disease, but the foregoing figures prove that it may be of immense benefit after the fifth day and later.

Theobald Smith, who prepares the antitoxin for the State of Massachusetts, gives the following account of his method: "At present the horse is universally employed to yield diphtheria antitoxin after a preliminary period of immunization with the toxin. Such animals must be free from any organic or infectious diseases, and mallein is employed to determine the presence or absence of latent glanders.

"The toxin used in the process of immunization consists of a bouillon culture of the diphtheria bacillus from which the bacilli themselves have been removed by sedimentation or preferably by filtration. The bacilli during the course of multiplication set free the diphtheria poison or toxin into the culture fluid. After one or more weeks of incubation the toxicity of the culture is at its maximum and it is then removed and stored for future use.

"The immunization is usually carried out by injecting subcutaneously at the start minute doses of this toxin and gradually increasing the dose, until the animal can stand, with but slight febrile and local reaction, doses ranging from 200 to 500 cc. After this preliminary treatment, which requires about three months, a little blood is drawn and the serum tested to determine the degree of antitoxic power which it has acquired. If this proves satisfactory the horse is bled regularly every four weeks, receiving in the meantime doses of toxin to maintain the toxin-neutralizing power of the serum on a satisfactory level.

"Horses differ markedly in antitoxin-producing power. Only a relatively small number yield antitoxin of a high potency under ordinary treatment and for long periods of time. Some horses may be made to yield a satisfactory serum, under conservative management, for four or five years. Others are debarred at the outset on account of inadequate toxin production.

"The withdrawal of blood is carried out with the usual aseptic precautions. A trocar with canula is inserted through a small skin incision into the jugular vein and the blood allowed to flow through sterile tubing into sterile glass jars. From five to eight liters are withdrawn each time.

"After the coagulation of the blood the serum is withdrawn, passed through Berkefeld filters into large bottles and stored until needed. Various antiseptics are added to the serum. Some add none. Chloroform in amounts not exceeding three-tenths per cent. has been found very satisfactory for the conditions governing free distribution in Massachusetts.

"Each lot of filtered serum is tested to determine its efficiency. Different quantities of the serum are mixed with that amount of toxin, which, according to special tests, is known to completely neutralize a standard Ehrlich unit of antitoxin. This mixture is injected into guinea-pigs, and the strength of the serum tested is estimated according to the result obtained. The serum is also tested bacteriologically for sterility and injected into guinea-pigs, although this latter test is hardly called for since the serum is usually kept so long after withdrawal that any disease latent in the horse at the time the blood is drawn (such as tetanus) would be detected in time for the rejection of the serum.

"Antitoxic serum, when kept in the cold and dark, deteriorates but very slowly. The sera of higher potency lose strength more rapidly than those of

lower potency. Precipitates usually form after a time, which are harmless, but which are occasionally mistaken by physicians for bacterial growth."

The standardization of antitoxin, by which is meant the estimation of the strength of the serum, is a complex process. According to Newman, Ehrlich has adopted as the immunity unit the amount of antitoxin serum which will neutralize a hundred times the minimum lethal dose of toxin, the serum and toxin being mixed together, diluted up to 4 cc., and injected subcutaneously. A normal antitoxin serum is one of which 1 cc. contains an immunity unit. An antitoxin unit is not a definite amount, but is that amount, be it greater or smaller, that will neutralize a given quantity of the toxin of diphtheria of a certain definite strength, and for this reason the dose is estimated by units and not by definite quantities.

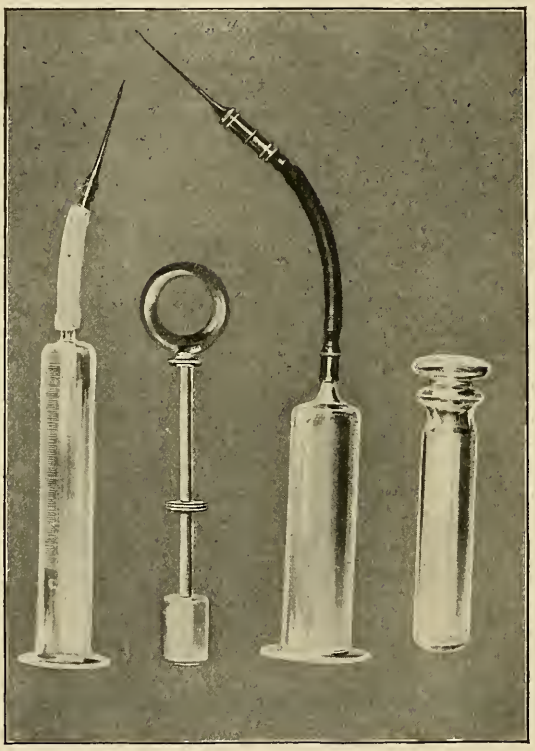
Mode of Administration.—Antitoxin is injected into the subcutaneous cellular tissue. The back near the angle of the scapula is the most desirable place, because in this locality the tissues are lax and, if unfortunately an abscess is caused, pus does not burrow to any great extent. Injections should not be given in the thigh, because the tissues are tense and the pressure of the fluid, therefore, causes great discomfort. If an abscess forms in this locality there is serious trouble from the burrowing of pus. Injections in the abdomen are inadmissible because they give discomfort. It hardly seems necessary to say that the injections should never be given in the arms or legs, were it not for the fact that the writer has seen serious trouble follow injections in these places. The intravenous injection of antitoxin has been advised, but there is no particular advantage in it, as the serum is readily absorbed in the subcutaneous cellular tissue. Antitoxin has been given by the mouth, but this method of administration is unscientific, utterly useless, and cannot be too strongly reprobated.

The syringe should be thoroughly sterilized by boiling and the site of the injection cleaned with the same care as for a surgical operation. A fold of the skin is taken up between the thumb and forefinger of the left hand, and the needle plunged quickly into the subcutaneous cellular tissue. When this is done there is comparatively little pain. The serum should be injected slowly and the tumor caused by it should be allowed to subside without rubbing. There are very many different syringes devised for this purpose. The simpler the syringe the better. The one used at the South Department is of glass with a glass piston and asbestos packing (Fig. 54, *a*). The needle is attached by means of rubber tubing. This is important, because the pliability of the tubing allows a certain amount of motion if a patient struggles, and therefore diminishes the liability of breaking the needle or the syringe. Luer makes a very good syringe with a ground glass piston (Fig. 54, *b*); the only objection to it is its expense. The piston should be removed from the barrel and the serum poured into it, because it is difficult to draw fluid through the needle. The piston should then be inserted, the syringe elevated and all air driven out. It is reasonable to suppose that some of the accidents that have been attributed to the injection of antitoxin have been caused by neglect of this precaution. The puncture should be sealed with absorbent cotton and collodion.

Dosage.—In serumtherapy the dose cannot be fixed by definite rules. Laboratory experiments do not give any assistance because it is known just how much of the toxin is to be antagonized by antitoxin, whereas in the treatment of the disease there is no known method of estimating the quantity

of toxin. Experience, and the clinical study of a large number of cases, are the only grounds on which sound conclusions can be reached. In the early days of antitoxin the doses were too small, for, as an unknown quantity was being used, the legitimate fear of doing harm was always present. As time went on and as there were no injurious effects due to the use of the serum, the dose has been gradually increased. The same rule holds good with antitoxin as with any other drug, namely, that the remedy should be given

FIG. 54.



a, Syringe in use at the South Department, Boston. *b*, Luer's syringe.

until the full therapeutic action is apparent. The duration of the attack of diphtheria has a very important bearing on the quantity to be administered. Statistics have already been given regarding the results obtained in the early administration of antitoxin. At the outset, if there is very marked congestion of the throat, even if there is no membrane or only a small patch, 4,000 units should be given. Except in very young children, age should have no influence on the dose. At the end of four or six hours, a second dose of the same size should be administered, and this should be repeated until the membrane has exfoliated and the congestion of the throat has disappeared. If there is very extensive membrane when the patient is seen for the first time, 8,000 or 10,000 units should be given, which should be repeated every four or six hours until the characteristic effect of the serum is produced, namely,

shrivelling of the membrane, diminution of the nasal discharge, a correction of the fœtid odor, and general improvement. No patient ill with diphtheria in the acute stage should be considered in a hopeless condition, but antitoxin should be given in large doses until he commences to improve or succumbs to the disease. When one sees a patient with membrane covering the tonsils and uvula, a profuse sanious discharge from the nose, spots of ecchymosis on the body and extremities, cold clammy hands and feet, a feeble pulse, and the nauseous odor of diphtheria, and finds that after the administration of 20,000 units of antitoxin in two doses the condition of the patient improves slightly, and after 10,000 units more there is marked abatement in the severity of the symptoms, that when an additional 10,000 units have been given the patient is apparently out of danger and eventually recovers, one must believe in serum therapy in the treatment of diphtheria. When one sees a patient in whom the intubation tube has been repeatedly clogged and the hopeless condition changes for the better after the administration of 50,000 units, one cannot but be convinced of the importance of giving large doses in the very severe and apparently hopeless cases.

Small doses of antitoxin are of little avail in the treatment of grave types of the disease and in order to obtain the best results, the serum must be heroically administered. It is true that all of the patients to whom large doses of antitoxin have been given have not recovered, but so many of them have that one must be convinced that large doses are imperatively demanded in very severe cases. When death has occurred, it has been from nerve degeneration or from sepsis.

Antitoxin has been conducive of much good in the treatment of diphtheria of the eye, the most serious acute disease with the exception of gonorrhœal ophthalmia. Serum should be administered in large doses—4,000 to 6,000, or even 8,000 units—every six hours until the membrane commences to disappear and the congestion of the eye diminishes. The pupil should be dilated with atropine and the eye irrigated every two hours with a 2 to 4 per cent. solution of boracic acid. The following ointment can be used with much benefit:

℞ Hydr. iodid rub.	gr. j	.065
Cocainæ muriatis.	gr. iv	.260
Atropiæ sulphatis.	gr. iv	.260
Petrolati	ʒj	30.

A portion of ointment the size of a small pea should be put in the eye every eight hours. Attention must be given to keeping the eye clean. If only one eye is affected the other must be protected by a watch-glass. A patch of membrane that in the throat would not be of importance, in the eye might cause blindness; therefore, the necessity of the early administration of antitoxin, where the condition of this organ points to diphtheria, is obvious.

Laryngeal Diphtheria.—Beneficial effects of the serum treatment in this are as marked as in the pharyngeal form. When a patient has a hoarse brassy cough with comparatively slight dyspnœa, but with rigidity of the sterno-cleido-mastoid muscles, antitoxin should be immediately given in large doses. It is generally conceded that about 90 per cent. of cases of laryngeal diphtheria previous to the days of antitoxin required operative interference. The investigations by the American Pediatric Society of the effect of the serum in laryngeal diphtheria occurring in private practice showed that only

39.21 per cent. came to operation. In hospital cases the proportion is larger, because the patients are received late in the course of the disease. It is, nevertheless, true that many cases of laryngeal diphtheria are relieved without operation by means of antitoxin, and the only reason that more are not relieved is the fact that antitoxin is not given early enough or in sufficient doses. Placing the child in a steam tent sometimes seems to be of benefit. Medicated steam occasionally gives relief. The following mixture in the proportion of one ounce to a pint of water may be used in the croup kettle:

℞ Olei eucalypti	℥j	30.
Acidi carbolici liq.,	℥j	30.
Olei terebinthinæ	℥viij	240. ℔

Only a limited amount of steam is required. A continued steam bath has a very debilitating effect, and this is always to be avoided. The air in the tent should be simply saturated with steam—not oversaturated. The sublimation of calomel has been used, but after a careful trial it seemed to the writer that it was of no particular benefit. Valuable time is lost and the strength of the patient lessened by vain attempts to get air into his lungs if these measures are continued for any great length of time. The chief reliance must be placed on antitoxin and operative interference.

If the dyspnœa increases, if the substernal retraction becomes more marked, operative interference is imperatively demanded. The question naturally arises whether tracheotomy or intubation shall be done.

Tracheotomy.—Tracheotomy is not a new operation by any means. Asclepiades, a Bithynian physician who practiced in Rome 100 B. C., was probably the originator of tracheotomy, or, as it was called at that time, bronchotomy. Paulus Ægineta, a Greek physician who lived in the latter half of the seventh century, gives explicit and clear directions regarding the operation. "We must make the incision in the trachea, under the larynx, about the third or fourth ring. This situation is the most eligible, because it is not covered by any muscle, and no vessels are near it. The patient's head must be kept back, in order that the trachea may project more forwards. A transverse cut is to be made between two of the rings, so as not to wound the cartilage—only the membrane." The idea of a transverse incision was based on the theory at that time prevalent that a wound of the cartilage would not heal.

In the Middle Ages tracheotomy does not seem to have been performed, as the medical literature of that time is silent on this point. In 1546 Brassavolo, physician to the Duke of Farrare, performed this operation successfully on a patient with suffocative angina, which was probably diphtheria. Fifty years later Santorio performed this operation with a trocar. This operation was termed at that time laryngocentesis, or, as it would be termed at the present time, plunge tracheotomy. In 1776 Vicq d'Azyr wrote regarding cricothyroidean laryngotomy. Home in 1765 recommended the operation. In 1782 tracheotomy was successfully performed by John Andree, a surgeon of London. Bretonneau, the historian of diphtheria, conceived the idea of making a large opening in the trachea and keeping it open with a metallic tube. Trousseau, the father of modern tracheotomy, had remarkable success in this operation, and his teaching popularized it. When, in 1848, he took charge at the Hospital des Enfants, Paris, the results in tracheotomy had been extremely unsatisfactory, 48 operations having been per-

formed without a recovery. From 1849 to 1858 in this hospital there were 466 tracheotomies performed with 340 deaths, giving 73 per cent of mortality. Trousseau devised the double tube which is now in use. Malgaigne was a bitter opponent of the operation. The controversy between him and Trousseau is extremely interesting reading. From this time until 1880, when O'Dwyer commenced his experiments on intubation of the larynx, a savage medical war was waged between the adherents and opponents of tracheotomy. The investigations of O'Dwyer brought a new factor into the controversy. If the operation of tracheotomy is done early in the course of an attack of diphtheria, the results are much more satisfactory than when it is done later. The operation, however, is not devoid of danger, particularly in very young children. The trachea in a young child is a very small tube; there are numerous bloodvessels in the operative tract; and the trachea is more deeply placed and situated beneath a thick layer of fat. These conditions render the operation extremely hazardous. The results obtained have not been particularly gratifying. As tracheotomy is an emergency operation, strict aseptic rules can not be followed. There is danger of infection not only from without but also from within. When possible, an anæsthetic should be given, but in the majority of cases the condition of the patient precludes general anæsthesia. Ether causes so much coughing that in some instances a little chloroform may be given, but, if given, the administration must be conducted with the utmost care. Local anæsthesia, with cocaine or ethyl chloride, can very frequently be used with satisfactory results.

There are three operations for opening the air passages: first, laryngotomy, where the incision is made through the crico-thyroid membrane; second, high tracheotomy, where the incision is above the isthmus of the thyroid gland; and third, the low operation, where the incision is made below it; the choice must depend on the age of the patient and the amount of swelling of the neck. The patient should have the head thrown back as far as possible in order that the trachea may become prominent. Incision should be made absolutely in the median line, and all bleeding vessels should be secured. When the skin and superficial fascia are divided, a careful dissection will bring into view a faint white line which is the raphe between the sterno-hyoid muscles. Any veins must be ligated or pushed aside. A careful dissection through the faint white line just described will expose the trachea. Retractors should be carefully held by an assistant, and the utmost care taken to avoid dragging with more force on one side than on the other. If the isthmus of the thyroid gland is exposed, it must be carefully pushed out of the way. The great size of this gland in children renders tracheotomy more difficult than in the adult. After the trachea is exposed, it should be opened by a careful cutting motion rather than a plunging motion. A probe-pointed bistoury is very useful for enlarging the opening in the trachea, as it is impossible with this instrument to injure the posterior wall. Bose's method of performing the high operation is described as follows: "The deep cervical fascia divides into two layers just above the superior margin of the thyroid gland, these two layers forming the main body of the thyroid capsule. The point of division corresponds exactly with the upper margin of the cricoid cartilage, which can be easily identified by touch. The nail of the left index finger is placed against the margin of the cricoid, the pulp of the finger looking downward, whereby the thyroid gland is protected, and

the fascia is opened by a short transverse incision directed against the upper edge of the cartilage. As soon as this is done, a blunt hook can be introduced through the transverse slit behind the thyroid gland, which then can be drawn down with some force, exposing the two or three upper rings of the trachea. The author never saw this method fail, and, in employing it, never was compelled to cut the cricoid cartilage for want of space to limit the incision to the trachea."

In performing the low operation, or inferior tracheotomy, the same general rules are to be observed. It must be a cardinal principle to stop all bleeding before the trachea is opened. Neglect to observe this rule has sacrificed the lives of patients. After the trachea is opened, Trousseau's dilator must be introduced into the wound, the blades opened, and the tube gently pushed into the trachea. No force must be used in inserting the tube. The incision must be long enough to admit the tube easily.

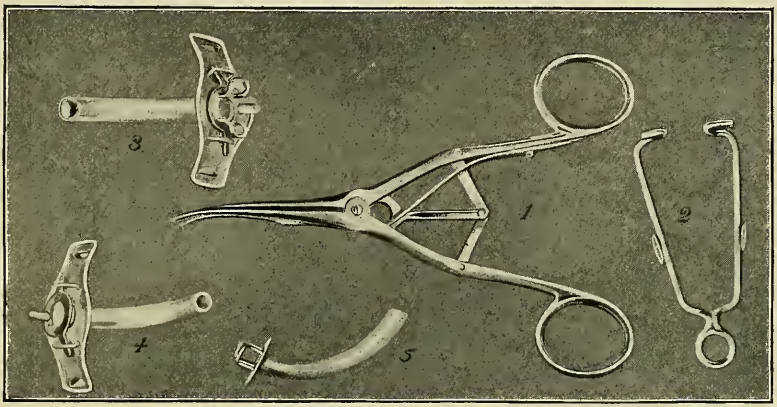
When tracheotomy is done in the later stages of diphtheria there is frequently an immense amount of swelling of the neck obliterating the surgical landmarks and rendering the operation much more difficult. The fact must also be remembered that, owing to the inability of the patient to get air into the lungs, not only the superficial, but the deep veins are in a very turgid condition; if they are cut, there is profuse hemorrhage which must be stopped before the trachea is opened. The directions given by some authorities, when the hemorrhage is profuse, to go boldly forward and open the trachea is not good advice, for many patients have died on the table from the blood flowing into the lungs. The instruments required for the operation are a scalpel, a probe-pointed bistoury, dissecting forceps, hæmostatic forceps, retractors, a sharp hook, Trousseau's dilator with three blades, and the tracheotomy tube. After the tracheotomy tube is secured in position by tape, the wound should be dressed with a thin cushion of sterile gauze cut so that it can be slipped under the collar of the tube. Before the introduction of the tube, if any membrane can be seen in the trachea, it should be removed with forceps. Great care must be taken in keeping the wound as clean as possible. The inner tube should be removed every two or three hours for cleansing, according to circumstances. Fig. 55 shows the dilator and a tracheotomy tube.

Plunge tracheotomy should never be done in patients under fifteen years of age, as in young patients the possibility of entering the trachea is very slight and the danger of wounding large bloodvessels very great. In adults in cases of emergency the operation may sometimes be justifiable. Different instruments have been devised for this purpose. In favor of plunge tracheotomy it may be said that, if the operator is fortunate enough to enter the trachea at the first plunge, there is no danger of hemorrhage, and the relief of the stenosis is immediate. On the other hand, there is great danger of missing the trachea and of wounding important structures. In the long run, the operation of tracheotomy by dissection is preferable.

After tracheotomy the irritation of the tube may cause sloughing of the trachea and adjacent tissues. Vegetations may form about the wound, seriously interfering with respiration, requiring that the tube be worn for an indefinite period. These sequelæ, however, are extremely rare. The tube should be removed at the end of three or four days even if it is necessary to reinsert it almost immediately. There is no definite time for its removal. Each case must be judged upon its merits.

Intubation.—In 1858, when Bouchut of Paris first conceived the idea of introducing a tube into the larynx through the mouth, the operation was not received with much favor. Trousseau strongly opposed it, and for nearly twenty-two years it fell into disrepute. In 1880 O'Dwyer, influenced by the alarmingly high death-rate of tracheotomy, commenced his experiments on intubation. For a long time the operation did not meet with the approval of the profession at large, but, as time went on, due to the persistent work of O'Dwyer of New York and Waxham of Chicago, intubation met with marked recognition in this country and is now the accepted operation of

Fig. 55.



1, Trousseau's dilator; 2, spring retractor; 3, tracheotomy tube; 4, outer tube; 5 inner tube.

election in cases of laryngeal diphtheria. In Paris in the hospital wards named for Trousseau, the most bitter opponent of the operation, intubation is performed in nearly all cases of laryngeal diphtheria. The French tubes are shorter than the American, but it is very doubtful if this is a distinct advantage. Bayeux says that intubation is the operation of election; that tracheotomy is the operation of necessity; that intubation originated in France, was improved in America, and finally was perfected in France. The latter statement must be taken with a certain amount of reservation. Much has been said regarding the causation of inhalation pneumonia after intubation, but the danger of this is more theoretical than practical. Northrup in the *Transactions of the International Medical Congress at Washington*, 1887, says: ". . . . The experiment has been tried of inducing 'schluck pneumonie' by feeding the child on milk and other fluids, having finely divided carbon in suspension. If this insoluble powder, having a strong contrasting color, were taken into the lungs in elective regions, it would be possible to find it later.

"In these experimental cases the powdered carbon (bone-black) was given while the child was able to swallow fairly well, so as to make the test satisfactory, and for the same reason it was discontinued when the child became enfeebled and was about to die.

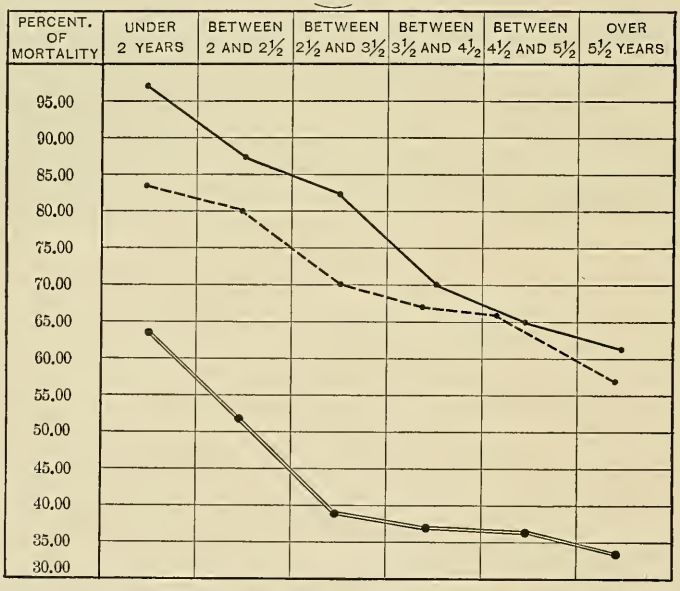
"I may say that I have never found any evidence that milk or bone-black had passed into the lungs of a child wearing a laryngeal tube. The smallest particle of milk bathing the under surface of a swollen and insufficient

epiglottis would excite violent cough. It does so in laryngeal tuberculosis in the adult."

It would seem as if these experiments of Northrup should be effectual in removing the fear of inhalation pneumonia as occurring as an accident in an intubed child.

Jacobi says that, previous to 1895, out of 1,024 operations of tracheotomy performed in various parts of the world, but principally in Europe, the mortality was 78.52 per cent. In the 327 tracheotomy cases at the Boston City Hospital from 1864 to 1887, the death-rate was 70.95 per cent. as given by Lovett and Munro. Stern of Philadelphia, in collating Bourdillat's statistics, gives the mortality of tracheotomy as 73.60 per cent. Waxham collected 1,072 cases of intubation performed in various parts of the United States, and gives the mortality as 73.23 per cent. At the South Department, from September 1, 1895, to December 31, 1904, the death-rate of the 1,553 intubation cases was 44 per cent. as compared with 73.60 in Bourdillat's tracheotomy statistics or with 73.23 per cent. in Waxham's intubation statistics.

FIG. 56.



Percentages of mortality of tracheotomy cases and of intubation cases without antitoxin and of intubation cases with antitoxin.

As showing the relative advantages of intubation with antitoxin as compared with tracheotomy without and intubation without, Fig. 56 has been prepared.

By following the full black line which represents the tracheotomy mortality rate and the broken black line which represents Waxham's intubations, and the parallel lines which represent the South Department intubations, it will be seen that the mortality rate of tracheotomy under two years of age was 97 per cent.; that Waxham's mortality rate of intubation previous to

antitoxin was 84.38, while that of the South Department was 64.98 per cent. Between the ages of two and two and one-half years the percentages were 88 for Bourdillat, 80.54 for Waxham, and 51.99 at the South Department. From two and one-half to three and one-half years the rates in the same order are 83, 70, and 39.97. Between three and one-half and four and one-half years of age Bourdillat's per cent. is 70, Waxham's 67.35, and at the South Department 37.89. From four and one-half to five and one-half years Bourdillat's is 65, Waxham's 66.08, and at the South Department 36.99. Over five and one-half years, 61 in Bourdillat's statistics, 56.67 in Waxham's and 34.97 per cent. at the South Department.

In analyzing the 685 deaths occurring in the 1,553 intubations at the South Department, it is found that bronchopneumonia caused 318 deaths, or 46.42 per cent.; that heart complications are responsible for 102 deaths; that the number of deaths from sepsis was 97; that extension of membrane into the bronchi caused 84 deaths. The total number of deaths from the causes just given is 601. The remaining 84 deaths were due to: scarlet fever occurring as a complication 24; measles 13; nephritis 21; pulmonary tuberculosis 6; cerebral hemorrhage 1; mediastinal abscess 2; clogging of tube 4; measles and whooping cough 2; fatty degeneration of the heart 4; diphtheritic necrosis of the larynx 1; abscess of the lung 5; unilateral internal hydrocephalus 1. There were 44 secondary tracheotomies with 5 recoveries. The tracheotomies were done as a last resort because intubation did not relieve the difficult breathing. When there was an autopsy, which was obtained in about 10 per cent. of these cases, the condition of the bronchi and lungs was such as to prove that, if tracheotomy had been the primary operation, the result would have been the same. Nearly 70 per cent. of the patients on whom the secondary tracheotomies were done were in a moribund condition at the time of entrance, and this accounts for the high death-rate.

Bronchopneumonia is always a very prominent factor in causing death in operative laryngeal diphtheria, but the mortality from this cause is not so high after intubation as after tracheotomy. The reason for this is probably that after intubation the air passes through the natural channels into the lungs, whereas in tracheotomy it does not. The deaths from heart complications, extension of membrane, and sepsis, would have occurred after any operative procedure and cannot be attributed, directly or indirectly, to intubation. Fatal clogging of the tube occurred only 4 times in the 1,553 intubations, and, therefore, it must be considered an extremely rare accident, but the possibility of its occurrence must always be considered. Accidents of a similar nature do occur after tracheotomy. Rejection of the tube by coughing occurred 566 times in the 1,553 intubations. In many of the instances it was necessary to reinsert the tube immediately. In other instances the patients would be from four or five hours without the tube, and then the dyspnœa would become so urgent that reintubation would become necessary. In still other cases, patients rejected the tube by coughing at the end of twenty-four to forty-eight hours and had no subsequent trouble, the convalescence being uneventful. This latter class is the most satisfactory of the intubation cases. There is no hard and firm rule regarding the length of time that an intubation tube should remain in the larynx. It is the writer's custom to remove the tube at the end of three or four days,

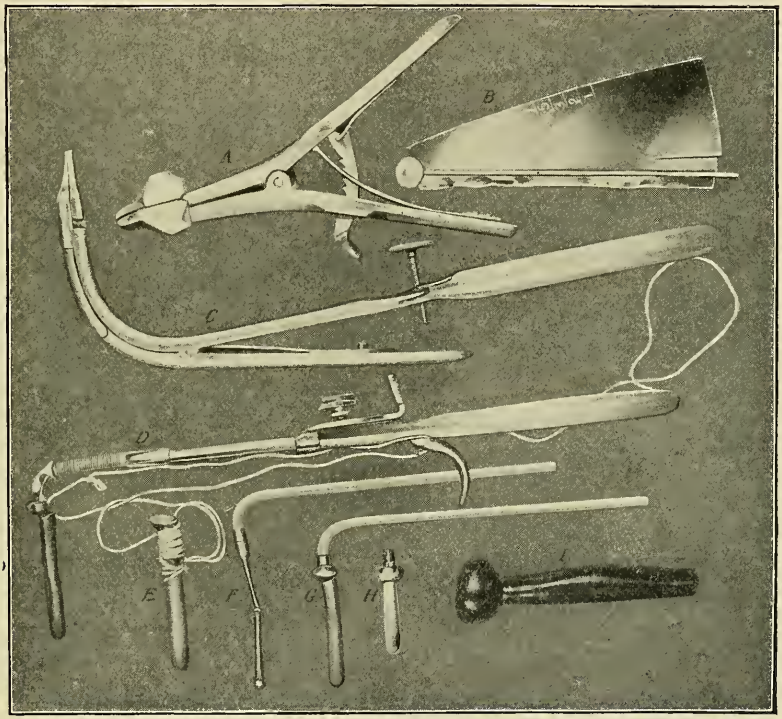
depending upon the condition of the patient; frequently, however, the tube has to be immediately reinserted. Sometimes an interval of eight or ten hours will elapse after the removal of the tube before the dyspnœa becomes so urgent as to require its reinsertion. The condition that causes dyspnœa sufficient to require reintubation may be spasmodic or due to collapse of the walls of the larynx weakened or paralyzed by the pressure of the tube. This latter condition must be differentiated from a stricture near the vocal cords, the result of traumatism in intúbation.

Much has been said, particularly by foreign observers, of the injurious effects of intubation. Strictures, false passages and adventitious growths have all been attributed to intubation; but if they were the result of the intubation, it was not the operation that was at fault but the operator. The liability of accidents and unfortunate sequelæ is very much less in intubation than in tracheotomy. A condition of the larynx due to stricture, the result of traumatism, requiring the permanent wearing of the tube, may sometimes occur, but a similar condition also occurs after tracheotomy. In 1,553 intubations at the South Department of the Boston City Hospital there were only 3 instances of this nature: One in which a subsequent tracheotomy was done and the patient left the hospital wearing the tracheotomy tube; 2 in which there was a stricture of the larynx which was yielding to treatment when the patients died of intercurrent bronchopneumonia in no way connected with the condition of the larynx. There were 4 other cases in which persistent intubation relieved the stenosis of the larynx, and the patients were discharged well. In one of these cases tracheotomy was done because the patient rejected the intubation tube by spasmodic coughing and was in such a critical condition before he could receive surgical attendance that it was deemed wiser to do a tracheotomy. He made a good recovery. In the other three instances the patients were intubated some thirty times. They made good recoveries, and one year after their discharge from the hospital there were no indications of any trouble with the larynx. A danger in intubation that is very much overestimated is pushing down the diphtheritic membrane by the tube. If the membrane is detached by the tube, the patient will very frequently, during a fit of coughing, expel not only the intubation tube, but a cast of the larynx. If there is no relief to the breathing after intubation, the tube should be immediately withdrawn, and frequently the patient will expel a large piece of membrane. Secondary tracheotomy is sometimes required, and, therefore, when an intubation is to be done, tracheotomy instruments should be in readiness. There is no operation that is so gratifying as an intubation when it is successful. One argument in favor of it is that there is no shock attendant upon the operation; a second is the fact that only a few minutes are required for its performance. When a child is pulseless and gasping for breath there is no time to wait for a careful dissection; air must enter the patient's lungs just as quickly as possible if his life is to be saved. The writer has seen too many patients brought into the operating room pulseless, cyanotic, apparently dead, who, after the intubation tube was introduced and artificial respiration performed, gasped a few times, then took longer breaths, soon commenced to breathe easily and naturally, and finally recovered, not to make him an earnest advocate of intubation. It is perfectly true that a patient after intubation requires more careful watching than one on whom a tracheotomy has been done, and for this reason, in sparsely settled districts, possibly tracheotomy may be better,

but in hospitals where there are skilled attendants constantly at hand intubation is the better operation.

Instruments.—The intubation set, as devised by O'Dwyer, consists of seven metal tubes or hard rubber tubes, an introducer, an extractor, a gag, and a gauge indicating the size of the tube according to age. The tubes have a large head to prevent them from slipping through the vocal cords. In the middle of the tube is a fusiform swelling, which is supposed to assist in keeping the tube in position. O'Dwyer's original tubes were made without this fusiform enlargement and he adopted this improvement later. In the French intubation tubes the introducer is attached to the obturator by a sliding joint, but this method has no particular advantage over that of O'Dwyer's. Hard rubber tubes are used to a certain extent, but, except in

FIG. 57.



O'Dwyer's separate instruments. (*a*) Gag; (*b*) gauge; (*c*) extractor; (*d*) intubation tube for a child two years old with the introducer ready for use; (*e*) intubation tube for a child three years old; (*f*) obturator showing a joint in the centre for easy removal after the tube is in position; (*g*) tube for a child one year old; (*h*) one of the French tubes for a child one year old. It is shorter than the O'Dwyer tube. (*i*) Tube for an adult, made of hard rubber.

instances where the tube has to remain in the larynx for a very long time, are no better than the metallic ones gold plated. The advantage claimed for the rubber tubes is that salts are not deposited on their surface. The writer prefers the metallic tubes, except in adults, in whom the weight of the metal may cause annoyance. Figure 57 shows the instruments in detail.

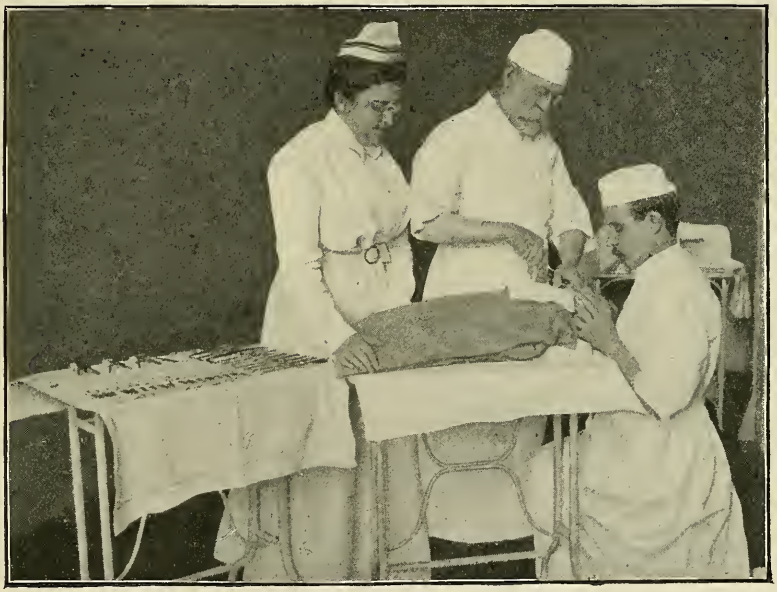
The question of feeding a patient after intubation is an important one. Œsophageal feeding may be required in certain cases. Nasal feeding should be abandoned except in rare instances, because it increases the possibility of middle-ear disease. The Casselbury method of feeding, which consists in placing the child on his back and lowering the head so that the pharynx is on a lower plane than the larynx, can frequently be adopted with advantage. Soft solids can sometimes be taken with ease. In the majority of instances sufficient food can be taken in the usual way if it is given slowly and in small quantities. The apparatus for œsophageal feeding consists of a soft rubber œsophageal tube and a glass funnel which is connected by glass tubing and rubber tubing with the œsophageal tube. The œsophageal tube is passed slowly and carefully into the stomach: the funnel is then elevated and the food is poured into it. As soon as the funnel is emptied, compression is made with the thumb and forefinger on the œsophageal tube, which is removed with a sudden quick motion in order to prevent reflex vomiting. In cases of nasal feeding, a soft rubber catheter of large size can be used.

The Operation of Intubation.—The patient's arms are placed at his side and he is wrapped in a blanket which is securely pinned. He is placed in a horizontal position with a small sand-bag under the neck. The gag is then inserted in the left side of the mouth with its jaws resting on the molar teeth, and firmly held by the left hand of an assistant who also steadies the head of the patient with his right. Great care must be exercised to prevent slipping of the gag. The operator then takes the introducer in the right hand with the index finger around the hook on the under surface of the handle, the loop of silk passing over his little finger and his thumb pressed against the button on the upper surface of the handle. The index finger of the left hand is then passed down to the epiglottis, which is hooked forward. The tube is then passed into the mouth with the handle well down on the chest of the patient. When the epiglottis is reached by the point of the tube, the handle should be given an abrupt turn upward so as to bring the tube into a horizontal position. As soon as the tube is pointed in the proper direction, the button on the upper part of the handle should be pushed forward disengaging the obturator, which must now be removed and the tube pushed into position by the index finger. The loop of silk is passed about the ear and the gag removed. If the tube is in the larynx the patient commences to cough with a peculiar sound. If the breathing is easier, the cyanosis disappears, the retraction of the thoracic walls diminishes, and the loop of silk does not shorten, it is certain that the tube is in the larynx. After becoming satisfied that the operation has been successful, the gag is inserted a second time, the index finger placed on the head of the tube, and one strand of the silk loop cut so that it can be removed. Remember that the left index finger of the operator must be a continuation of the posterior wall of the larynx; remember to make the abrupt turn; remember that no force must be used. If the tube is in the œsophagus, no cough will be heard; there will be no relief to the breathing; the silk loop will commence to shorten as the tube passes down the œsophagus. If the tube becomes clogged by membrane it must be immediately removed, and after this the patient will frequently reject a large piece of membrane by coughing.

The first steps of an extubation are similar to those of an intubation. The extractor is passed into the lumen of the tube, the lever on the handle pressed so as to open the jaws, and the tube extracted by a reverse of the

movement in introduction. Extubation is sometimes more difficult than intubation but by gentleness and patience it can be accomplished. There are records of cases where the intubation tube has been pushed down so far into the trachea that tracheotomy was necessary to accomplish its removal. This is so rare an accident that it cannot be used as an argument against intubation. A patient may sometimes expel the tube from the larynx and swallow it. This is an annoying occurrence, but not one of any special gravity, as the tube is always passed by the rectum in twenty-four to seventy-two hours. Instances have occurred where the intubation tube has been forced by coughing into the nasopharynx and removed with great difficulty but this is extremely rare. Bayeux describes a method for removal of the tube by digital pressure or, as he terms it, by enucleation. The operator places his right thumb on the larynx of the patient just below the intubation tube and with the left hand the head of the patient is thrown back; then with a quick motion the head of the patient is brought forward, and at the same

FIG. 58.



Position during intubation.

time upward pressure is made upon the intubation tube, which is expelled through the mouth. Bayeux says this method is particularly adapted for the short tubes. The writer has used it several times with the O'Dwyer tubes with satisfactory results. The great advantage of this method is that it can be used by a trained nurse in an emergency, as when the tube suddenly becomes clogged and no physician can be reached.

Fig. 58 shows the position of a patient during intubation. In certain parts of the country it is customary to intube in the upright position, but experience has taught the writer that the horizontal one is the better both for the patient and the operator. Intubation of an adult is a difficult operation, but can be successfully accomplished with very satisfactory results.

If twenty-four or forty-eight hours after operative interference for laryngeal stenosis, when all the indications have been favorable, there is a sudden rise in temperature, a profuse tenacious mucopurulent discharge from the tracheotomy tube, or the intubation tube is clogged with a similar discharge, it is evident that membrane is extending to the bronchi, and therefore large doses of antitoxin should be administered. The failure to recognize the gravity of the condition just described and neglect in administering large doses of antitoxin at this time are responsible for many fatal results in operative laryngeal diphtheria. These points cannot be too strongly emphasized.

It is advisable, but not essential, to place the patient on whom tracheotomy has been done in a steam-tent; it is not necessary to have a great amount of steam. Three or four layers of gauze saturated with corrosive sublimate, 1 part to 5,000, over the entrance to the tracheotomy tube will moisten the air sufficiently before it enters the lungs. A patient after intubation does not require steam except in rare instances.

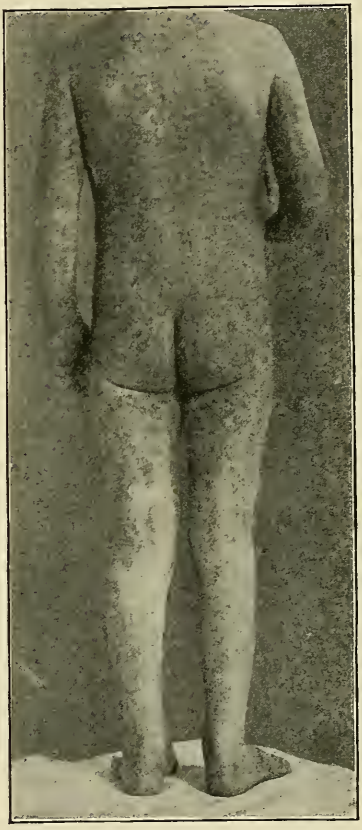
Alleged Injurious Effects of Antitoxin.—A great deal has been said regarding the injurious effects of antitoxin. Many of the statements show a deplorable ignorance of the natural history of diphtheria. It is frequently said that antitoxin has a depressing effect on the heart. If one reads carefully the earlier writers on diphtheria he will find that failure of the action of the heart was known and recognized long before the days of antitoxin. Flint, in his *Practice of Medicine*, published in 1866, alludes to this condition as do many other authorities. Theoretically there is no reason to assume that antitoxin should have any injurious effect upon the heart. Practically it has been demonstrated that this organ is not affected in any way by the serum. It has been claimed that paralysis is caused by antitoxin. This statement is only an instance of attributing a certain symptom to the remedy used when it is a part of the disease treated. It would be well for the critics of antitoxin to read some of the older medical works in order to become convinced of the fact that postdiphtheritic paralysis was known long before antitoxin was used. Albuminuria has been attributed to the serum. Wade of Birmingham, England, in 1857, first called attention to the existence of this symptom in diphtheria. Abeille found that it occurred in 33 per cent. of his cases in one year. In investigating this subject the writer examined the urine of 173 patients ill with diphtheria, before and after the administration. It was found that albumin was absent in 99 instances both before and after the administration of the serum. In 33 instances, although albumin was present before the serum was given, it was not increased after its administration. In 25 the albumin was diminished, which seems a sufficient reply to the claim that antitoxin causes albuminuria. In 16 instances the albumin was increased, but not to a sufficient extent to cause anxiety. As these were severe attacks of the disease, the conclusion that the albuminuria was caused by the toxin of diphtheria, and not by the remedy, is justifiable.

It must be conceded that arthralgia in a certain proportion of cases is due to the use of the serum. This condition sometimes causes a certain amount of discomfort to the patient, but in no instance in the writer's experience has it ever given rise to a serious train of symptoms. Rashes frequently are caused by antitoxin. They are of four types: erythematous, scarlatiniform, morbilliform, and urticarial. The urticarial is the most annoying of these eruptions and frequently the patient will have great discomfort from itching

for two or three days. The temperature is frequently elevated. Urticaria appears in about 30 per cent. of the patients injected with antitoxin. The amount of the serum used does not seem to influence the prevalence of this eruption. Small doses will be followed by urticaria just as frequently as the large doses. Certain horses seem to furnish serum that gives rise to a large number of cases of urticaria. For the relief of the itching in the rash of the urticarial type the usual remedies are of benefit. The morbilliform eruption very rarely gives rise to much annoyance and does not require any special treatment. The scarlatiniform eruption is very frequently mistaken for

Fig. 59.

Fig. 60.



scarlet fever, and the difficulties of a differential diagnosis for the first twenty-four hours are very great. There may be a slight rise in temperature, but, as a rule, there are no subjective symptoms. The erythematous eruption may be of two varieties, either a simple erythema, or an erythema multiforme. In the simple erythema there may be a slight rise in temperature, but the patient does not experience much, if any, discomfort. In erythema multiforme there may be a slight burning of the skin and a moderate rise in temperature; itching is very rarely observed. Fig. 59 shows a general

eruption of erythema multiforme. This patient had no constitutional disturbance due to the eruption. Fig. 60 shows the same eruption after it had commenced to fade.

All of these eruptions are followed by a certain amount of desquamation, but it is not nearly so profuse as that following scarlet fever. Errors in diagnosis, so far as scarlet fever is concerned, have been made based on a hasty conclusion that because a patient desquamates, therefore he must have had scarlet fever. The time for the appearance of these eruptions varies greatly, the limits being from ten minutes after the injection of antitoxin to five weeks, with an average period of about ten days. It is not the antitoxic element that causes these eruptions, but the serum, and the stronger the serum, or, in other words, the greater number of antitoxin units to the cubic centimeter, the less is the probability of these cutaneous manifestations. Various accidents have been attributed to antitoxin, but their connection with the serum is extremely problematical. That accidents may occur during the administration of antitoxin, that certain anomalous symptoms may follow, but not necessarily be due to antitoxin, that the serum may be impure, must be taken for granted; but these events occur after the use of any remedy that is potent in the treatment of disease.

It is inconceivable in the light of the enormous weight of testimony based on statistics how any one can have any doubt regarding its efficacy. An experience based upon the treatment of over 15,000 cases of diphtheria convinces the writer that antitoxin must be considered one of the greatest medical discoveries of the nineteenth century, comparable with the protective power of vaccination; and also that antitoxin must be given in large doses in order to accomplish the most beneficial results.

Immunization.—If antitoxin is the deleterious agent that it is assumed to be by certain observers, if there is any danger from its use—the immunization of individuals against possible infection with diphtheria would be unjustifiable. Results have demonstrated, however, not only that the serum when given for immunization has no injurious effect, but that outbreaks of diphtheria in the children's wards of different hospitals have been prevented. In the Children's Hospital in Boston, where no infectious diseases are admitted, from May, 1897, to March, 1905, during which time 9,694 patients were treated, each patient under two years of age was immunized with a dose of 750 units of serum, and each child over two years of age was given 1,500 units. Previous to May, 1897, the wards and sometimes the whole hospital had to be closed on account of outbreaks of diphtheria. T. M. Rotch says that he does not hesitate to give the serum even when the patients are quite ill, and that he never has seen any bad results beyond the appearance of certain efflorescences.

In the Infants' Hospital in Boston, where children not over two years of age are treated, immunization was commenced in February, 1900. Before this, outbreaks of diphtheria were very frequent among the babies and also among the nurses and nursery maids. Since immunization was begun there has been only one case of diphtheria among the babies which was thought to have originated in the hospital. At the present time a dose of 500 units is given instead of 300 units, which was used at the outset. From February 1900, to March, 1905, 1,185 patients were treated in this institution. As a control it is interesting to know that a number of nurses and nursery maids

have in the years just mentioned contracted diphtheria, but they had not been immunized, as they preferred not to be.

It is a well-known fact that patients ill with scarlet fever are particularly susceptible to diphtheria, and that frequent outbreaks of the latter disease occur in scarlet fever wards. For the past five years in the scarlet fever wards of the South Department every patient is immunized with a dose of serum of from 1 to 2,000 units, depending upon the age. The result has been that there has been no outbreak of diphtheria in these wards, although there have been a certain number of positive cultures with no constitutional manifestations. Immunization lasts only about twenty-one days, and, therefore, it is necessary to reimmunize at the expiration of this time.

The beneficial results of antitoxin in the treatment of diphtheria would seem to have been sufficiently demonstrated to convince the intelligent practitioner of the importance of using this remedy in the treatment of each and every case of diphtheria. The statements regarding immunization should also be convincing.

CHAPTER XV.

WHOOPING-COUGH.

By JOHN RUHRÄH, M.D.

Synonyms.—Pertussis (Sydenham); tussis convulsiva; Kink-cough; chin-cough; French, coqueluche; German, Keuchusten; Spanish, tossferina; Italian, pertosse.

Definition.—Whooping-cough is a contagious disease characterized by a paroxysmal or spasmodic cough usually ending in a long sonorous inspiration and frequently accompanied by vomiting. Cullen's famous definition was, "Morbus contagiosus, tussis convulsiva strangulans cum inspiratione sonora iterata, saepe vomitus."

Historical.—It is not certain that whooping-cough was described by the ancients, and it is not mentioned by writers in the middle ages. It seems safe to assume that it did not exist at that time, as such a distinctive disease could hardly escape accurate description. The epidemics of cough noted by many of the early writers were undoubtedly influenza. The first accurate description was given by de Baillou, in Paris (1578), and in England it was mentioned by Thomas Willis (1658) and by Sydenham (1679). During the eighteenth century it was more frequently described, the studies of Plaz (1727) and Friedrich and Hoffman (1732) being among the most notable. During the nineteenth century it was very common, and now it is endemic in most of the large cities, and epidemics are so common as to be regarded as unworthy of mention except by statisticians.

The geographical spread is interesting. It started in Paris in 1578, was noted in London in 1658 and in Germany in 1724. A severe epidemic involved all of Europe in 1732 and 1733, and the disease was carried to America. In 1847 it was introduced into New Zealand, and about 1890 into Australia and the Archipelago.

Etiology.—Epidemics vary greatly from year to year in virulence, intensity and mortality. The disease is more severe and frequent in cold climates; otherwise epidemics are apparently unaffected by season and weather conditions, although the course is less severe in weather which permits children to be out of doors. Epidemics of great severity and mortality have been seen in the summer. Susceptibility is very general, and the majority of persons have the disease. The greatest predisposition is from six months to five years of age, and over half the cases occur during the first two years of life. As the individual grows older the susceptibility decreases; but the disease is seen in adults and even in old age, Hale White having reported a case in a woman aged eighty-one years. During the first months of life the disease is not common, although it may be seen, even in the newly born. Watson records a case where the mother had been taking care of a child with whooping-cough and her own child showed symptoms of the disease on the first day. Bouchut observed a child who developed a cough on the second day and showed unmistakable signs of whooping-cough on the

eighth day. Girls are said to be more susceptible than boys, and children who are weakened by disease are more liable than strong healthy ones, and the disease is more severe in the weak. In nervous children the paroxysms are always more severe. Wimmer and Meissner state that the deaf and dumb and the blind have the disease in a milder form than children with normal senses.

There are three theories regarding the causation. Some regard it as a neurosis and others as a laryngo-tracheal catarrh; but the disease is generally regarded as one of the infections. The question as to the organism of whooping-cough can not be definitely answered at this time. Poulet (1867), Letzerich (1870) and Tschämmer (1876), are among the earlier observers who mentioned organisms as a cause. Burger, in 1883, called attention to a short bacillus, fully described in 1887 by Afanassiew, which was found in the sputum and produced symptoms in dogs. Ritter, in 1892, isolated a diplococcus which he claimed to be causal, and was also able to produce symptoms in young dogs. In the following year Cohn and Neumann described a streptococcus as the cause. Deichler has described a ciliated protozoan, which he found in the mucus, and Behla, Henke, Kurloff and others, believe that the cause of the disease is some form of protozoan. Czaplewski and Hensel, Koplik, and Walsh, have all described an organism which they isolated from the mucus, especially in the earlier stages of the disease This organism is a short bacillus, easily stained in carbol-glycerine-fuchsin, and readily grown on blood serum. Another organism, resembling the influenza bacillus, was described by Spengler, in 1897, and later by Jochmann and Krause, in 1901 and 1903. This has been called the *Bacillus pertussis Eppendorf.* It was isolated from cases of bronchopneumonia occurring with whooping-cough, but could not be demonstrated in ordinary cases of pneumonia. Spengler is of the opinion that the organism is the same as that described by Czaplewski and Hensel despite the apparent differences, and there is much to support this view. Elmassian, Luzzatto, and other observers, have described somewhat similar bacilli.

Wollstein investigated thirty cases of whooping-cough and found a bacillus which is apparently identical with the *Bacillus pertussis.* It grows in media containing hæmoglobin, and apparent differences are doubtless due to technique. Agglutination tests with Wollstein's bacillus were positive. It is closely related to the influenza bacillus, but can be separated from it by means of agglutination reactions. Leuriaux has described a short bacillus, ovoid in shape, found in the expelled mucus. This organism produces a virulent toxin by which Leuriaux has produced an antitoxin in the horse, which he has used in treatment.

Jahn and others called attention to the fact that domestic animals may be affected by whooping-cough and that they may be the means of transmitting it to children. It is most frequently observed in dogs, but has also been noted in the cat. An instance of a canary bird exposed to pertussis having a spasmodic cough has also been recorded.

The disease is usually transmitted by direct contact, and only a very short exposure is necessary for infection. In some instances it would seem that being in the immediate neighborhood without direct contact was all that was necessary; but in these the child may have been infected by flying particles of sputum. The infectiousness begins with the earliest symptoms, and is more intense early in the disease than later, although it may be trans-

mitted even in the late stages. Morse attempted to determine whether the disease was transmitted by indirect contact by gathering the experience of forty observers. The consensus of opinion was that it happened but rarely. That transmission by fomites is possible is instanced by the following classic case: A woman whose two children had whooping-cough was on a ship which touched at St. Helena, and the children's clothing was sent ashore to be washed. The children of the washerwoman contracted the disease, although there was said to be no whooping-cough on the island at that time.

Infectiousness varies in hospitals and is most liable to occur when the patient enters early in the course of the disease. If the children mingle together indiscriminately, especially where there is overcrowding, an epidemic is sure to occur. If the beds are far apart, with plenty of air space, and the children are kept separated, the liability to infection is much less. If the sputum is carefully looked after, infection may be even avoided altogether, as has been pointed out by Eustace Smith and Grancher.

Recurrences are rare, although clinicians of large experience may see one or two such instances; for example Rilliet and Barthez report 2 cases, Trousseau 2, and Comby 1.

The incubation period is difficult to ascertain owing to the indefiniteness of the early symptoms. From one to two weeks usually elapse from the time of infection to the onset, but this may be considerably less. If sixteen days pass and the disease has not made its appearance, the chances are that it will not develop.

Pathology.—There is more or less congestion and catarrhal inflammation of the mucous membranes of the larynx, trachea and bronchi, and the severe coughing may produce emphysema. The lower surface of the epiglottis is also involved by the inflammation. Von Herff was able to see the larynx during paroxysms, and noted that the mucous membrane became dark-red and was covered with transparent mucus. A small pellet of yellowish mucus about the size of a pea then made its appearance, and the coughing continued until this was dislodged. The coughing also frequently produces a small ulceration of the frenum of the tongue in children who have cut their teeth. The fatalities are caused by complications such as convulsions or pneumonia.

Symptoms.—Whooping-cough has three stages: *i. e.*, a catarrhal stage, or the invasion, a paroxysmal or spasmodic stage and the stage of decline or defervescence.

Catarrhal Stage.—The invasion is general. The child has a slight bronchitis, which cannot be distinguished from an ordinary cold, often complains of headache or of general malaise, and there is often coryza, with sneezing and increased lachrymation. Huguenin has called attention to the photophobia, with which there may be dilatation of the pupils. There is often a slight rise in temperature toward evening, but this usually ceases before the spasmodic stage begins. There may be muscular pains of considerable severity. Redness of the pillars of the fauces and pharynx has been described by de Mussy, but it is not characteristic. The catarrhal stage lasts from one to two weeks and then passes into the spasmodic stage. Some children whoop almost from the beginning; others may not do so for over two weeks, and some not at all. There may be occasional paroxysms of coughing during the catarrhal stage, and a persistent cough, especially at night, should always arouse suspicion.

Spasmodic or Paroxysmal Stage.—The fever and catarrhal symptoms disappear, the cough becomes more and more paroxysmal, and in nearly all cases the characteristic long inspiration or "whoop" is heard. The child usually feels a paroxysm coming on, either in an indefinite way or there may be a sense of constriction about the chest or of oppression about the heart. The child runs to the mother or nurse for support, or grasps the nearest object, and if there is nothing near, both hands grasp the legs near the knees to brace the body for the approaching attack. There is a severe barking cough often of a loud metallic character, the face becomes reddened and cyanotic, the eyes are suffused, and the veins of the neck and head stand out prominently. All the muscles of the chest are brought into action. During the coughing there is protrusion of the spoon-shaped tongue. After a series of explosive coughs, there is the prolonged noisy whoop, and after one or several of these a small ball of tenacious mucus is expelled, very frequently with vomiting. In adults the paroxysms are less severe as a rule, although at times they may be very troublesome. The anxiety at the beginning of the spasm is not so marked, but in neurotic patients it may be as great as that in children. Some adults are unfit for business from general nervousness during the attack, whilst others are but little affected except during the periods of coughing.

The average number of paroxysms is about twenty in twenty-four hours (Trousseau). Tissier records a case in which in a three-year old child on the seventh day there were one hundred and twenty paroxysms. The duration of each paroxysm varies, and it may last only a few seconds, with a single whoop, or be prolonged for as much as fifteen minutes, with between fifteen and thirty whoops. The paroxysm may be brought on by excitement and irritation of various kinds. The attacks, as pointed out by Heberden, are less frequent in good weather than in bad. Attacks which come on after eructation, vomiting, or the passage of flatus, are lighter than usual, but the succeeding paroxysm is of usual severity. Cough of a paroxysmal character may be caused by imitation, and a whole school may be set to coughing by a patient with pertussis. In a ward full of whooping-cough patients all may cough at the same time, a paroxysm in one child bringing it on in the others. The whoop may be entirely absent and the cough merely of a paroxysmal character, as is common in young infants. The whoop may also vanish with the appearance of inflammatory diseases, notably pneumonia, meningitis and diphtheria. Vaccinia is said to have the same effect.

The paroxysms may cause hemorrhage, or the sphincters may relax with involuntary passage of urine or fæces. After the attack the child may be utterly exhausted and remain in a half-conscious condition; others have a fit of crying; sometimes after the paroxysm the child may be at once ready to return to play. Cases have been reported where the paroxysms of coughing were replaced by attacks of sneezing. The paroxysmal stage persists usually from a month to six weeks, although it may last only two or three weeks; or, in severe cases, much longer. In overcrowded institutions and when the child does not get any fresh air, the paroxysms continue much longer than under more favorable circumstances.

Decline.—The cough loses its paroxysmal character and becomes less frequent. After excitement, emotions, or violent exercise, it may become paroxysmal again for a short time. It may also return after an attack of indigestion or following a heavy meal. For some months any attack of

bronchitis is liable to be more or less paroxysmal in character. This stage lasts from one to several weeks.

The Urine.—The urine, according to Cima, contains an increase in the amount of uric acid. Gill, Johnston, and others, found glycosuria in 16 out of 100 cases. Bendetti claims that the glycogenic function is lowered in pertussis and that very slight excesses of sugar cause glycosuria.

The Blood.—Frolich, Meunier and others, have studied the blood in whooping-cough. They found that there was a constant leukocytosis, which begins early, before the paroxysmal stage, continues through it, and disappears with it. The leukocyte count varies between 20,000 and 25,000 in the average case, but may run as high as 40,000. All forms are increased, but the principal increase is in the lymphocytes. A blood examination is of great diagnostic value in whooping-cough.

Crisofi found the iodophilic reaction in 80 per cent. of the leukocytes, chiefly in the polynuclear neutrophiles, less frequently in the eosinophiles, and rarely in the lymphocytes.

The Skin.—In whooping-cough, besides purpura, there may occasionally be vesicular or pemphigoid eruptions. Furunculosis is also seen.

Duration.—Epidemics in cities generally last ten to twelve weeks, but they may often persist for six months or even a year. In the largest cities the disease is endemic. The duration of the attack is variously stated, and differs greatly in different epidemics from four to six weeks, from seven to ten weeks, and from sixteen to twenty weeks. Average figures are: Incubation one week, catarrhal stage one to two weeks, paroxysmal stage four to six weeks, and decline two to three weeks.

Complications.—These are numerous and deserve more attention than they usually receive.

Misuse of Drugs.—This is a frequent cause of symptoms sometimes erroneously attributed to whooping-cough. The most frequent are drowsiness, or even unconsciousness, from narcotics; delirium; dry throat and mydriasis of belladonna; and tinnitus, gastric disturbance, rashes, and other symptoms, from overdosing with quinine.

Other Infectious Diseases.—Measles, scarlet fever, and diphtheria, all of which are unusually virulent in children suffering from whooping-cough, are chiefly to be feared (Comby).

Hemorrhage.—This is frequent from the severe coughing spells causing rupture of the swollen vessels. Epistaxis is not infrequent. Ecchymoses into the conjunctiva are frequently seen, but this requires no especial treatment, disappearing in from two to four weeks. Ecchymoses of the eyelid may also occur either on one or both sides. Conjunctival hemorrhage may cause bloody tears. Small hemorrhages may take place from the ear, either due to rupture of the drum or from the external auditory meatus. Rupture of the tympanum may occur, but as a rule causes only temporary inconvenience. Hemorrhage under the skin results in petechiæ or ecchymoses, and hemorrhage may also take place from ulcerations, nævi, or recent scars, or from the lips, gums, and ulcer of the frenum. Hæmoptysis and hæmatemesis are rare. Hemorrhage may be found in the pleura, cerebrum, kidney, adrenals, and other organs at autopsy. Abortion and metrorrhagia are rarely caused by whooping-cough.

Respiratory Tract.—Œdema of the glottis has been reported by Barthez and Sannée. Spasm of the glottis, the so-called *convulsion interne* of the

French, is rare. In this condition the breathing ceases after expiration, the face swells, the body becomes cyanosed, and the child may fall unconscious and a convulsion follow. The attack ends with a long crowing inspiration and the child breaks out in a profound perspiration. This condition may prove fatal.

Bronchitis is always present during the catarrhal stage, but may be regarded as a complication during the spasmodic stage and defervescence. Congestion of the lungs is not infrequently seen, and is often described as abortive pneumonia. With it fever symptoms like the initial stage of lobar pneumonia, and sometimes even slight dulness, are found; but the condition clears up in a day or two. Bronchopneumonia is the most frequent serious complication and is the cause of nine-tenths of the deaths. It may occur in the very young, in whom it is a particularly fatal complication. Lobar pneumonia is rarer and not so fatal. Pleurisy may be seen occasionally, and an effusion may be present. Bronchiectasis occasionally follows whooping-cough, and is said to be frequent after measles and whooping-cough together. Acute emphysema is present in nearly every case, and extreme grades may be met with. There may be rupture of the lung and cutaneous emphysema.

Alimentary Tract.—Catarrhal conditions of the stomach and intestines are frequent, and diarrhœa is not uncommon. The so-called mucous disease if present is always aggravated; or, if children have had it, recurrence may be looked for. Prolapse of the rectum may occur, and hernia of any variety may be caused by the severe coughing.

Kidneys.—Albuminuria may be present in some cases. Acute parenchymatous nephritis is a rare complication.

Nervous Complications.—These are numerous and have been studied by various observers. Paul Valentin gives the following classification:

1. Psychoses.	*a*. Delirium, hallucinations. *b* Depression of spirits (apathy). *c*. Imbecility.
2. Neuroses.	*a*. Hysterical attacks. *b*. Epileptiform attacks. *c*. Choreiform and other convulsive attacks.
3. Motor Troubles.	*a*. Convulsive: *e. g.*, eclampsia, cramps, and spasm of glottis. *b*. Paralytic: *e. g.*, hemiplegia, monoplegia, and aphasia.
4. Sensory Troubles.	*a*. Anæsthesia. *b*. Deafness. *c*. Blindness.

Rhein[1] has also made a very satisfactory study of the subject and has collected the literature.

Psychoses.—Meschede has reported a case of a child with hallucinations of sight, hearing and touch. Delirium has also been observed. Depression and apathy may occur, and Möbius had a case of melancholia. There may be mental deterioration and imbecility, while epilepsy and chorea have been reported after whooping-cough. This last may sometimes be due to intracranial hemorrhage.

[1] *Journal of the American Medical Association*, 1905, p. 697.

Cranial Nerves.—Blindness may follow hemorrhage, or optic atrophy and deafness may occur from the same cause. Paralyses of the various motor nerves, evidently due to hemorrhage, have been reported. The sixth nerve has been involved, evidently from hemorrhage into the pons, and paralyses of the crico-arytenoid muscles have occurred.

Convulsions.—These may be general or limited, especially in children about the age of teething. Twitching of groups of muscles, particularly those supplied by the facial nerve, may be seen.

Cerebral Hemorrhage.—In Valentin's thesis 83 cases were collected. Of these 16 were monoplegia, 40 hemiplegia, and 5 or 6 paraplegia. The lesion in some was found to be hyperæmia, in others punctate and larger hemorrhages, whilst in some no lesion was noted. In 21 cases the location of the lesion was as follows: Brain, 7; between the dura and the skull, 2; meninges, 1; brain substance and meninges, 2; capillary hemorrhage, 2; hyperæmia, 4; no change, 3.

In Valentin's cases there was paralysis in 79 cases. In 64 the result is stated as follows: Cured, 28; deaths, 14; incurable, 22. Valentin attributes the hemorrhage more to the toxæmia than to the paroxysms. The location of 42 cases collected by Hochenjos showed: Meninges, 6; cortical, 2; central, 8; ganglia, 6; location not given, 24. Leroux collected 38 cases, and of these 25 were under five years of age. Möbius has recorded an interesting case in which there was a hemiplegia with considerable mental disturbance. The paralysis cleared up, followed by a return of intelligence, in about four months. George S. Brown has reported a case of subdural hemorrhage in which the clot was removed by operation, with complete recovery.

Other Lesions of the Brain and Cord.—Numerous other conditions have been reported. Encephalitis has been noted and also sclerosis. Cerebral diplegia may follow whooping-cough; Foggie has reported such a case. Bernhardt has reported a child aged five years who after a paroxysm became stiff in the legs, but this finally disappeared entirely. Hagedorn had a case in which there was paraplegia, then ptosis and spasm of the facial muscles. Later there was complete paralysis and finally death. Möbius has reported a case of ascending (Landry's) paralysis in a child aged three years in which complete recovery took place. The author regarded it as a case of multiple neuritis. A case of hydrocephalus has been reported as following whooping-cough.

Peripheral Nerves.—Neuritis from whooping-cough has been studied by Eshner and Aldrich. There have been but few cases reported; Eshner collected six, including the case of Möbius referred to above.

Diagnosis.—This is rarely difficult after the disease has thoroughly developed. In the catarrhal stage there is little to separate it from an ordinary bronchitis except the presence of the lymphocytosis. The possibility of infection is also a point of some value, and the occurrence of the disease in the family, school, or friends of the patient, should always be sought. A virulent cough in a child who has never had whooping-cough is always suspicious, especially if it is prolonged and frequent at night. The blood examination is important. As soon as the spasmodic stage is reached there is little difficulty. If the child does not have a paroxysm in the presence of the physician one may be brought on for diagnostic purposes by the following method suggested by Guida: Hold the child as for a throat examination;

then introduce a spoon along the teeth, and when the child opens the mouth carry the spoon to the base of the tongue in such a manner that the epiglottis comes into view. A paroxysm is produced, and this is more severe in whooping-cough than in any of the conditions which may be mistaken for it.

Variot suggested a more painful procedure for bringing on a paroxysm; namely, passing the finger into the mouth as in doing an intubation, raising the epiglottis, and pressing upon the larynx.

The spasmodic cough heard in children with enlarged bronchial or tracheal glands is more like whooping-cough than the cough heard in any other condition. Barthez and Sannée give the following table of differential points:

Whooping-Cough.	Enlarged Glands.
1. Contagious, epidemic.	1. Isolated, not contagious.
2. Three periods, second paroxysmal.	2. No distinct periods.
3. Paroxysmal cough with whoop, vomiting and viscid expectoration.	3. Paroxysms short, frequent without the whoop, expectoration or vomiting.
4. Respiratory sounds normal.	4. Signs of enlarged glands sometimes present.
5. Respiration normal in interval, apyrexia if simple.	5. Asthma in some cases alternating with paroxysms. Febrile movements with recrudescence in the evening, sweats, progressive wasting, etc.
6. Voice natural.	6. Sometimes a change in voice.
7. Usually acute.	7. Chronic.

In hysteria there may be a spasmodic cough, but this lasts longer, and there may be bloody expectoration. Croup comes on suddenly and wears off by morning, to recur usually for several nights. Acute œdema of the glottis is attended by inspiratory dyspnœa, aphonia, and shock. Laryngismus stridulus has no prodromes, and is often accompanied by carpopedal spasms, and the course of the disease is different. Spasmodic cough may occur in catarrhal laryngitis, with elongated uvula, adenoids, and enlarged tonsils. Paroxysms of coughing not unlike whooping-cough may be caused by foreign bodies, such as feathers, pebbles, etc., in the larynx, trachea, or bronchi. The coughing ceases when the foreign body is dislodged. Ictus laryngicus, or the so-called laryngeal vertigo, is attended with a spasmodic cough. There is a burning sensation in the larynx, cyanosis, and the patient falls to the ground. The arms and legs are relaxed or twitch convulsively. Recovery is rapid.

Prognosis.—According to the older writers whooping-cough was a very fatal disease. In England the mortality is still rather high. In America the disease is regarded as a mild affection, notwithstanding that in 1900 there were 9,958 deaths from whooping-cough, a higher mortality than from scarlet fever. The older the child the more favorable is the prognosis. In nurslings and children under three years of age the outlook is serious. It is stated that nine out of every ten deaths are due to pneumonia. The other causes of death are inanition due to loss of sleep and constant vomiting, hemorrhage into the brain, external hemorrhage, asphyxia, syncope, convulsions and bronchitis. Death has resulted from secondary nephritis. In overcrowded institutions the disease is prolonged and fatal, and this is also true wherever there is overcrowding and lack of fresh air.

Prophylaxis.—The spread of the disease should be prevented by isolating the child. The room should be disinfected if it is to be occupied by a young

child. Especial care should be taken to avoid infecting young children and those with other diseases. There are no measures which will prevent an individual taking the disease, if he is susceptible, except the avoidance of infection. The patient should be regarded as a source of infection until the spasmodic stage is over.

Treatment.—Much can be done to make the course of the disease less severe but it is extremely doubtful if any treatment has an influence in shortening the duration. The peasants in Southern Germany have a saying that it continues until it stops. There is scarcely a disease in which as many drugs and therapeutic measures have been recommended, and it would require several pages to enumerate them. On the other hand, there are many physicians who unfortunately agree with the dictum, attributed to Franck, "You can kill a whooping-cough child before the affection has run its course; you can never cure him."

Hygienic Measures.—These are of great importance. The child should lead a quiet, out-of-door life, free from all excitement. The more the child is in the fresh air the less severe the disease. The sleeping-apartments should be thoroughly aired during the day and well ventilated at night. If the child cannot be out of doors, owing to his condition or bad weather, it should be taken from room to room and not allowed to spend all the time in one unaired room as is so frequently done. As far as possible the temperature should be even and the child protected from extremes and also from winds, dust, and irritating vapors. The clothing should be suited to the weather. The child should be clothed with sufficient warmth, but not be burdened with extra wraps either by day or night. In cold weather the bed should be warmed before the child is put into it, as contact with cold sheets is liable to bring on a paroxysm. The child should not be bathed too much during an attack of whooping-cough.

The diet should be light and nourishing. Younger children may be put on an exclusive milk diet, and this should also be done whenever there is much vomiting. The feeding may become a very serious problem, and it should be the first care from the onset of the disease. If one meal is vomited, another should be given immediately, as each paroxysm is usually followed by a period of comparative quiet. In such cases the amount given should not be too large. Rectal enemata may be used if necessary, and even subcutaneous injections of oil in extreme cases. Great care should be taken not to upset the stomach with nauseating drugs.

Psychic treatment is of some value, and the child should be instructed to cough as few times as possible. Most of the paroxysms come on spontaneously, but some nervous children do an unnecessary amount of coughing. Strong emotions may bring on or cut short paroxysms, and the number may be diminished by fright. Severe punishment, which should under no circumstances be used, is recorded as sometimes influencing the disease.

Anything which reduces the number of paraxysms or cuts them short is of great value, as it lessens the danger from prolonged and severe coughing. Nägeli has suggested an ingenious method of stopping the paroxysms. This consists in pulling the jaw forward and downward in the manner frequently employed by anæsthetists. This can be done by the mother or nurse every time the child feels a paroxysm coming on. Kilmer recommends a snugly fitting elastic band applied about the abdomen. This he claims lessens the number of paroxysms and the vomiting. It is applied as follows: A stock-

inette band, similar to those used under plaster jackets, is applied to the body from the axillæ to the pubes and two shoulder straps are used to keep it from slipping. On this stockinette a width of silk elastic is sewn so that it goes around the body and covers the entire abdomen. The elastic is of the same quality as that used for stockings and in older children two widths may be necessary. It should be pinned slightly on the stretch and then sewn on so as to keep it from curling.

Mohn, of Norway, advocates frequent disinfection with sulphur of the room occupied by the patient. He claims to have cut short the disease by this method. Formalin disinfection has been used for the same purpose and formalin vapor in a very dilute form has been suggested as a method of treatment. Compressed air-chambers have been devised, and good results are claimed by certain writers. A number of observers claim that anti-diphtheritic serum injected several times during the disease lessens its severity and shortens its course.

The idea that vaccination influences the course of whooping-cough dates from Jenner's time. Poschi advises vaccination at the beginning of an epidemic. He states that it has no curative effect after the disease has passed the initial stage, but has when it is practiced during incubation. Recent vaccination protected those who had been recently exposed, but children vaccinated a year previously were not protected.

Inhalations, sprays, and insufflations of powders have been recommended. Among the best inhalations are creosote, oil of eucalyptus, and carbolic acid vapors. A dram (4 gm.) of any one of these is added to a pint (500 cc.) of water and the steam inhaled. Sulphurous acid obtained by burning sulphur pastilles is also used. Bravo and Soltman use cypress oil. This is diluted with alcohol 1 to 5, and from 2 to 3 drams (8 to 12 gm.) are poured on the pillow or underclothing four times a day. Of the sprays, 2 per cent. solutions of salicylic acid or resorcin are the most highly lauded. The throat is sprayed every two or three hours, the child being told to breathe deeply while it is being done. Local applications of various kinds are made to the nose and throat.

Internal Medication.—Much can be done to render the patient more comfortable and lessen the number of paroxysms. No one drug acts equally well in all cases and the effect of any drug may diminish if used continuously, but after stopping it for some time it may be resumed with benefit. Any medication causing nausea or vomiting should be stopped immediately. The following are the most useful of the numerous drugs recommended: Heroin hydrochloride is one of the very best, as it quiets the cough and exerts a sedative action. It is best given in an elixir in doses of gr. $\frac{1}{100}$ to $\frac{1}{24}$ (0.00065 to 0.0027 gm.) four to six times a day. Belladonna is given as the tincture, in doses of from 1 to 10 minims (0.06 to 0.6 cc.) four or five times a day. A small dose should be given at first and this increased until slight flushing is observed about twenty minutes after it is administered. This dose may be continued. Blonds require much smaller doses than brunettes. Delirium, mydriasis, and dryness of the throat, may be caused if the dose is too large, or in very susceptible individuals. Antipyrine is a most valuable drug. It should not be given too continuously nor when the heart is weak. It may be given in doses of 1 to 5 grains (0.0625 to 0.324 gm.). Codeine sulphate may be added to this with advantage. From gr. $\frac{1}{60}$ to $\frac{1}{4}$ grains (0.001 to 0.016 gm.) may be used, according to the age of the child. For younger

children it is best given in syrup of orange; older children may take it in capsules.

Quinine, as suggested by Binz, is of considerable value, especially in older children; but the large doses in younger children are liable to cause nausea. It is given in doses of about gr. $\frac{1}{6}$ (0.01 gm.) for each month of the child's age, and about gr. $1\frac{1}{2}$ (0.1 gm.) for each year of the age. This dose should be given four times a day. In some children the effect on the cough is remarkable; in others the poisonous effect of the drug precludes its use. Aristochine has been highly lauded by Kettel. He advises gr. $1\frac{1}{2}$ (0.095 gm.) for each month of the child's age, three times a day, the dose not to exceed 15 grains (1.0 gm.) under one year of age nor 30 grains (2.0 gm.) in older children.

Camphor was recommended by Max Jacobi in 1804, and still has many advocates. Its chief value is probably due to the stimulating effect. Croton chloral hydrate is advised by Eustace Smith. He gives 1 grain (0.06 gm.) every two, three or more hours, according to the age of the child and requirements. It is often useful to add to this a double quantity of potassium bromide. Fluoroform has recently been used by Stepp and others, apparently with excellent results. A 2 to 2.5 per cent. aqueous solution is used, and of this ʒ 1 to 2 (4 to 8 cc.) is given every hour or two. It sometimes causes slight pharyngeal irritation. Bromoform is of great value in lessening the number and severity of the paroxysms, but there is danger of poisonous effects from overdosage. It should not be prescribed among ignorant or careless people. From 1 to 5 drops may be given at a dose. Emulsions should be thoroughly shaken before each dose. It is best to drop the drug on sugar. Neumann observed that the sputum becomes thicker as the cough diminishes and suggests that medicaments be given to thicken the sputum and so lessen the cough. Excessive vomiting can sometimes be relieved by cocaine given twice daily. About gr. $\frac{1}{6}$ (0.01 gm.) is given at a dose.

Leuriaux has produced an antitoxin serum which he claims to have used with success. Kelaiditis also claimed to have a curative serum.

CHAPTER XVI.

MUMPS.

By JOHN RUHRÄH, M. D.

Synonyms.—Parotitis epidemica; Latin, cynanche parotida; French, les oreillons; German, Ziegenpeter.

Definition.—Mumps is a specific infectious disease characterized by fever and by swelling and tenderness of the salivary glands, usually of the parotids, but sometimes of the submaxillary and sublingual glands. Metastases occasionally occur in other organs.

History.—Mumps was described by Hippocrates. In 1761 Hamilton called attention to the orchitis, and Mangor, in 1773, recognized it as being a contagious disease.

Etiology.—Mumps occurs in epidemics, especially in schools, colleges, and barracks, and is endemic in the larger cities. Epidemics are apparently uninfluenced by weather or climate, and the sexes are about equally affected.

The majority of the cases occur in children between five and fifteen years of age. Under five years the susceptibility to the disease is not great, and after fifteen it apparently diminishes with age. Nursing infants are usually immune and may not contract the disease even when nursing the breast of a woman with mumps; but cases have been reported during the nursing period. The disease may be transmitted through the placental circulation. White relates a case of a woman whose child showed signs of the disease six days after delivery, and the woman herself had swelling of the parotid on the following day. Comby cites a case in which a woman eight months pregnant developed mumps, and her child, born at term, showed marked swelling of the parotids and had difficulty in swallowing. After increasing for two days the swelling gradually disappeared. Individuals of sixty or seventy years are not immune, and cases may occasionally be seen at that age.

Epidemics in institutions are usually slow and last several months, new cases developing from time to time; from one-quarter to one-third of those exposed take the disease. This varies in different epidemics and with the age of the individuals exposed. Barthez and Sannée report 230 cases out of a school of 540

The disease is transmissible evidently before the symptoms appear, and for some time, even as long as six weeks, after they have disappeared. Transmission is usually by direct contact, and the disease is not transmitted through the air and only rarely by a third person or by fomites. Roth relates a case contracted by sleeping in a bed previously occupied by a patient with mumps, and instances are on record where a nurse was the means of infecting other persons.

Epidemics in institutions and barracks are often confined to one set of buildings or to one enclosure. In a small epidemic, in the writer's experience, in an institution with four groups of children, the disease confined itself to one group, although no care was taken to prevent the spread of the disease

beyond keeping the children apart from the others. The same corridors were used, the attendants went about freely, and the clothes were sent to the laundry without disinfection.

Incubation Period.—This is usually long and is variously stated by observers. Roth placed the average at eighteen days, with a minimum of four days and a maximum of twenty-five days, whilst the commission appointed by the Clinical Society of London set the incubation from fourteen to twenty-five days. It may safely be asserted, however, that the average period is nearer three weeks than two. There are undoubted cases in which the disease has developed after thirty-five days (Parker Douglas), and even after six weeks (Bernutz).

Immunity.—One attack generally confers immunity; but second attacks are by no means rare, and even third attacks have been reported several times. Out of 230 cases Barthez and Sannée report 20 recurrences and 3 third attacks.

Bacteriology.—A number of organisms have been described. The most interesting and complete report is by Laveran and Catrin. They obtained an organism in pure culture by puncturing the parotid gland, from the testicle, the œdematous tissue, and the blood. The organism was a micrococcus occuring in pairs (diplococcus), which grew on ordinary media and was easily stained but was decolorized by Gram's method of staining.

Pathology.—But few opportunities have been afforded for pathological study. There is an intense hyperæmia and œdema of the gland, with considerable infiltration around it. There are no subsequent changes in the gland.

Symptoms.—Prodromes may or may not be present. They are usually noted in about one-third of the cases, and come on from twelve hours to two days before the swelling appears; but in some cases there may be prodromes from four to even eight days. The usual prodromes are fever with or without a chill, general malaise, vertigo, drowsiness, vomiting or diarrhœa, and epistaxis, and there may also be sweats, fainting spells, pain in the ear, and trismus. The symptoms proper are principally the glandular swelling, pain, and fever. The parotids are usually affected and one or both sides may be involved. The gland enlarges rather rapidly for from three to six days, then remains stationary for a day or two, and gradually subsides. The subsidence is usually complete in a week or ten days, although in severe cases it may be three weeks or a month before the enlargement has disappeared entirely. The left side is more frequently affected than the right, and where both sides are not affected at the onset the opposite side is generally involved in from one to four days. In some instances it may be a week or more before the other side enlarges, or only one gland is affected. All grades of intensity may be seen, and there may be light cases which could be very properly termed abortive. In these there is slight fever with a little tenderness and swelling which disappears in three or four days. The average case presents a large rounded swelling at the angle of the jaw, with the lower edge of the lobe of the ear at its centre. The swelling is somewhat boggy at first but does not pit on pressure. Later it becomes very tense, rather firm, and the skin over it is stretched and glazed. In some cases there is a little redness, most marked just back of the ear, while in others there is a considerable blush of the skin and exceptionally an almost erysipelatous redness.

In the most severe forms, which are rather rare, there may be enormous swelling and œdema of the tissues which may extend all around the neck and

head and as far as the outer end of the clavicle. These patients present a grotesque, unrecognizable appearance.

The submaxillary glands may be affected after the parotids are invaded. In some cases the submaxillary glands alone, or the submaxillary and the sublingual glands, may be attacked without any involvement of the parotids. The sublingual glands are less commonly affected, although, like the submaxillary, they may be attacked after the parotids or even by themselves without any further lesion. The sublingual tissues may be involved without any distinct glandular involvement, a condition which has been described by Henoch.

Pain is almost a constant symptom although exceptionally absent. It is located in the swollen gland, back of the jaw, in the temporo-maxillary articulation, and often down the neck. Canstatt, according to Barthez and Sannée, called attention to pain down the neck and in the region of the scapula. The pain is increased on pressure, on mastication and salivation, and is rendered acute by taking acids, as lemon juice or vinegar, into the mouth; and even the sight of them may cause pain in neurotic subjects.

The throat cannot be said to be involved except in severe cases, when there may be swelling due to the œdema. The tonsils may be pushed inward by this and if large may render swallowing very difficult. Some authors have described an enanthem, but this may be regarded as a complicating stomatitis.

Fever is nearly always present. It may precede the swelling or come on about the same time, and usually ranges from 102° to 103° F., but may be much higher. It disappears as the swelling subsides or sometimes several days before. After an attack of mumps there may be a subnormal temperature for some days. The jaw is usually stiff and in some cases the trismus may even precede the swelling. The saliva may collect in the mouth owing to a slight increase in the secretion and the difficult or painful swallowing, while in other cases there is a decrease in the saliva and consequently a dry mouth. This is a symptom of which some persons complain considerably. In unusual cases there may be little or no pain, fever, or constitutional disturbance, and the swelling in such cases is usually slight.

Complications.—These are numerous and vary greatly in different epidemics. In one epidemic one particular complication may be quite frequent, as epistaxis, while in other epidemics another complaint, as abdominal pain or diarrhœa, may be common.

Metastasis.—Other structures of the body may be involved, most frequently the testicle in the male, and in the female, tenderness of the breasts, ovaritis, and swelling of the labia majora. Swelling of the inguinal glands may occur in both sexes.

Orchitis.—Exceptionally this may occur early, before the parotids are affected; and instances have been recorded where in epidemics it was the only lesion. As a rule orchitis begins at the time when the parotid swelling is subsiding; but it may come on after the parotid swelling has disappeared entirely. There is a return of the fever and constitutional symptoms, and these latter are often severe, although occasionally absent. The testicle swells, becomes tender and painful, and the swelling continues for three to five days or longer and then subsides. Following such an attack there may be atrophy of the testicle. Orchitis is uncommon in infancy and not often seen until puberty or later. Ovaritis occurs in the same way. There is pain in the

pelvic region, with swelling and tenderness of the ovary, and this lasts about the same length of time as orchitis. The breasts may become swollen, hard, and painful in a similar manner, and males as well as females may be affected. The prostate may be involved and cases of urethritis have also been reported. Other glands may occasionally be affected, as the thyroid, which becomes swollen and tender. There may be swelling of the lachrymal glands.

Pancreatitis.—Pancreatitis is a little-studied complication, but Simonin has reported 10 cases occurring in 652 cases of mumps. The symptoms came on between the first and twelfth day, usually between the third and sixth day, and lasted from two to seven days. There was pain between the xiphoid cartilage and the umbilicus, sometimes radiating along the costal arches and even into the interscapular, dorsal, or lumbar regions. Palpation was impossible on account of the pain. There was nausea and vomiting, and diarrhœa occurred in one-half the cases. The fever was irregular and was absent in 4. Cuche states that he found tenderness over the pancreatic region in 20 out of 26 cases.

Ocular Complications.—These are chiefly of an inflammatory nature. There may be conjunctivitis, keratitis, ulcerative keratitis, iritis which may leave synechiæ, retinal congestion, and optic neuritis. Optic atrophy may follow the neuritis. There may be photophobia, lachrymation and chemosis. External œdema about the eyes, with marked chemosis, may render the patient well-nigh unrecognizable. Madonnet has reported a case where there was paralysis of accommodation and of the uvula, and Campari had a case in which there was hemeralopia which lasted five days and then gradually disappeared.

Ear Complications.—The most frequent of these is deafness. Texier has collected 34 cases following mumps and in 17 it was bilateral. In many there was buzzing in the ears and tinnitus. In 13 cases there was vertigo lasting from a few hours to a few days, and in 4 cases there was vomiting. The deafness may be due to middle-ear trouble or to central disease, and in the latter case the prognosis is bad. The deafness comes on about the fourth or fifth day—sometimes as late as the tenth or fifteenth day. Otitis media is rarely seen following mumps. Hemorrhage into the labyrinth has been reported.

Nervous Complications.—Symptoms resembling meningitis may come on, and these may follow orchitis. Complete recovery is the rule, but paralysis, aphasia, difficult articulation, agraphia, and other sequelæ, have occasionally been noted. Facial paralysis has been reported. There may be very marked delirium even in adults. Curious cases of aphasia and paralysis may be seen; 1 of aphasia with paralysis of one arm lasting five days has been reported. Lannois and Lemoine have reported cases in which there was aphasia and right hemiplegia which remained several months. R. F. Smith has recorded a case of acute mania following mumps. Multiple neuritis has also been observed. Monod has found that there is a spinal lymphocytosis in some cases of mumps, and he thinks that there is some close relationship between the meningeal condition and certain nervous symptoms, as bradycardia, headache, herpes, and meningeal symptoms.

Respiratory Complications.—Inflammatory conditions of all parts of the respiratory tract have been met with, such as coryza, bronchitis, congestion

of the lungs, and lobar or bronchopneumonia. Œdema of the glottis may be a dangerous complication, especially with widespread œdema.

Cardiac Complications.—Following the attack there may be a slow or intermittent pulse, and with this a low temperature. Syncope may be noted. Endocarditis and pericarditis are rare complications.

Renal Complications.—Miller has collected 30 cases of nephritis following mumps. It is more common in males, and is of a moderately severe type, lasting usually a week or more and usually ending in recovery; but some deaths have been reported. Chronic nephritis occasionally follows the acute attack. The nephritis generally comes on early in convalescence, but it may be four or five weeks after the attack before it manifests itself. Albuminuria is common during the febrile stage, and hæmaturia, uræmia, and anasarca, have all been noted in the nephritis of mumps. Miller suggests especial precaution against exposure. Sylvester has reported a remarkable case in which after a severe onset the swelling and tenderness of the parotids disappeared in twenty-four hours; swelling and tenderness of the kidneys followed with cessation of the renal function and the presence of cerebral symptoms. Recovery took place, but on the eighth day an orchitis appeared.

Joint Symptoms.—Occasionally there may be pain or swelling of the joints and bursæ. Septic arthritis with suppuration has been reported, but such an occurrence should lead to a doubt as to the correctness of the diagnosis.

Blood.—Pick reports the blood findings in mumps to be a slight relative increase in the mononuclears at the height of the disease, but no leukocytosis.

Diagnosis.—This is as a rule easy—the history of exposure, with a large swelling, the centre of which is the tip of the lobe of the ear, usually suffices. It is differentiated from enlarged lymphatic glands by the position of the swelling, as in mumps the little hollow between the mastoid and the jaw is completely filled, whilst in adenitis the swollen gland is lower down. Non-specific parotitis frequently suppurates, especially if it occurs in pyæmia.

Other Forms of Parotitis.—One should bear in mind that swelling and tenderness of the parotid may occur from numerous causes other than mumps. These non-specific enlargements may be classified as follows:

a. Following or during infectious diseases. Typhus fever, typhoid, pneumonia, scarlet fever, and diphtheria, may be specially mentioned; but swelling of the gland may occur in any infectious disease. These are almost always infections, and suppuration is very common. It is not very rare with syphilis.

b. From septic infections, most commonly after pelvic and peritoneal inflammations, appendicitis, cystitis, and pyelonephritis. In these cases the affection may be sympathetic or due to infection.

c. Following disease or injury of the abdominal or pelvic organs, and rarely from operations upon other parts of the body. Barlow called attention to this in 1886, and the subject has been reviewed by Bunts.[1] Parotitis occurred 5 times in 200 cases of ovariotomy, 4 of which suppurated. The submaxillary and sublingual glands may also be affected. Bucknall gives the following list of operations which have been followed by parotitis, even though the operation was entirely aseptic: Exploratory laparotomy, gastrotomy, and other operations upon the stomach; enterectomy, colotomy;

[1] *American Journal of the Medical Sciences*, 1904, page 803.

hernia operations; ovariotomy; operations upon uterus and tubes; renal operations; operations on the liver and gall bladder. To this list may be added castration, or the operations or injuries of the testes, the insertion of a pessary, the passage of a catheter, excision of hemorrhoids, and amputation of the leg. Delivery, abortion, menopause, or disorders of menstruation, may also be followed by parotid enlargement.

d. In chronic diseases, as diabetes, and any grave form of asthenia, and in the general paralysis of the insane. Symmes has called attention to chronic bilateral parotitis occurring in the insane, and reports 5 cases, all over thirty years of age. Three of these patients had syphilis and all showed stigmata of degeneration.

e. In chronic poisoning, as that due to mercury, lead, or the iodides.

f. In association with facial paralysis, as in the case reported by Gowers.

g. In Mickulicz' disease, in which there is enlargement of the salivary and lachrymal glands, coming on without any apparent cause, and persisting.

h. In gaseous tumors of Steno's duct such as are seen in glass-blowers and musicians.

Prognosis.—As a rule this is good. Occasionally one of the complications leaves a permanent lesion behind it; deafness is one of the most frequent of these. Suppuration rarely occurs. The cases in which suppuration and gangrene have been reported are either not mumps or are due to accidental infections. Stewart has reported a death from syncope on the fifth day, previous to which the breathing had been asthmatic. Atrophy of the testicle may follow the orchitis, or there may be a lack of development of the testicle if the attack occurs before puberty. This is usually only upon one side, but it may in some instances be bilateral. In these latter cases virility is usually retained.

Treatment.—Mumps is a self-limited disease, little influenced by treatment. Much can be done, however, to make the patient more comfortable and to relieve pain. The food should be liquid, or soft, so that it may be easily swallowed without mastication. Acids and highly seasoned foods should be avoided. A mouth wash should be used to keep the mouth clean, as brushing the teeth may be impossible. The external application of heat is grateful to many patients. The swelling should be anointed with an ointment or a glycerine application to render the stretching of the skin less disagreeable. Various medicaments are mixed with these. Five per cent. guaiacol in an ointment, or glycerine may be used. Belladonna is highly recommended. Methyl salicylate may be applied to the gland three or four times a day. Internally a dose of calomel or a saline should be given at the onset, and the bowels kept open during the attack. Anodynes may be given if necessary. Tonics, especially iron, may be used during convalescence.

CHAPTER XVII.

INFLUENZA.

By FREDERICK T. LORD, M.D.

Historical.—Opinions differ concerning the first account of influenza. An epidemic in 412 B.C., described by Hippocrates and Livius, may have been influenza. The epidemic of 1510 is the first which has received universal acceptance. Again, in 1557 there was a general outbreak of the disease, and in 1580 the first great pandemic is reported. Four well marked epidemics occurred during the seventeenth and ten during the eighteenth century. During the nineteenth century there were four great pandemics: 1830–32, 1836–37, 1847–48, 1889–90. Hirsch, however, mentions fifty-three years in which epidemic influenza occurs between 1800 and 1875, and Ripperger notes seven years between 1875 and 1889. A survey of the *Index Catalogue* shows that not a year has elapsed from the last great pandemic to 1902 without a record of local outbreaks in some part of the world.

The scanty reports from the earlier times cannot be regarded as indicating an absence of influenza, which may always have been as prevalent as in the last century. Following many of the extensive epidemics, it has been repeatedly observed that the disease recurred at varying intervals, at times lasting for several years.

Epidemiology.—It is difficult to trace the origin and course of the different epidemics, especially the earlier ones. Some of the great pandemics, notably the last, afford evidence of a general direction from East to West. The distribution of the disease has been variable, from local to general diffusion, at times covering the greater part of the globe as true pandemics. Even before 1889–90 it was noted that the disease prevailed without relation to the climate, wind, weather, or telluric conditions. In rapidity of progress the outbreaks exceed that of any other known disease, and were thought too rapid to admit of contagion from person to person.

A careful statistical study was made of the last great pandemic and valuable data were obtained by numerous collective investigations. Among the most notable productions was the report on 55,263 cases in the German army, on 22,972 cases in Munich (where notification was compulsory), and *Parson's Local Government Report.* Leyden and Guttmann's report of the German Collective Investigation represented an enormous amount of work. G. B. Shattuck's and Abbott's studies in Massachusetts were the most painstaking in America. Leichtenstern's account of the disease in Nothnagel's *Handbuch,* which has been used freely, is the most complete in the literature.

1889–90.—The origin of this pandemic, like many others, is uncertain. The outbreak in Hongkong in the fall of 1888, in Buchara in the middle of May, 1889, or in Tomsk in the beginning of October, may have been the starting point of the epidemic which occurred in St. Petersburg toward the end of October. By November the disease had swept through Germany and France; by December through Austria, Sweden, Denmark, Switzerland,

Italy, Spain, Portugal, Belgium and the Netherlands, England, the Balkan States, and North America. By March, it had reached India and Australia; by April and May, China and the Gold Coast of West Africa. Berlin was invaded the middle of November, Paris from the 17th to the 20th of November, London the second week of December, Boston and New York the 17th of December. Within a year it had visited nearly all parts of the world.

Scarcely was the pandemic of 1889–90 ended when small local outbreaks reappeared in a few places. In the winter of 1891, however, an extensive epidemic occurred in the United States and the North of England, but seems largely to have spared Europe, with the exception of small scattered local outbreaks. A direct relation between these isolated infections could not be established, and they seemed to come from local sources. Again in the fall of 1891 and spring of 1892 there was a third outbreak, this time again reaching the proportions of a true pandemic.

A study of the reports of the first great pandemic of 1889–90 from all parts of the world showed that the disease had not spread, as had been previously believed, faster than modern modes of conveyance, but rather followed the lines and did not exceed the rapidity of human intercourse. A succession of scattered cases preceded and led up to the epidemic in the regions attacked. The principal commercial cities or larger garrisons were first invaded, then the smaller places and the neighboring country. On boats the disease first appeared after touching at an infected port. Institutions little in communication with the outside world, such as prisons, convents, and lunatic asylums, were often spared or affected later than the neighboring population. When cases did occur they were at first often exclusively among those having intercourse with the outside world. Thus the great mass of evidence is in favor of the direct transfer of the disease from person to person.

In the two later epidemics a more irregular course was followed; the spread from place to place could no longer be traced. The disease diffused more gradually and lasted longer in a given neighborhood. Fewer persons were attacked.

Morbidity.—In general about 40 per cent. of the population were attacked in the first great pandemic, thus repeating the experience of previous outbreaks and maintaining a record equalled by no other disease. Though no age is exempt, infants and old people seem least disposed to infection. The relation of age is apparent in the Munich cases, where of 22,972 persons affected, about one-half were between twenty-one and forty and about one-third between twenty-one and thirty years of age. Males and the robust members of the community seem more susceptible, probably because of their more frequent exposure.

Duration of Epidemic.—The invasion period, from the recognition of the first cases to the beginning of the epidemic, was usually fourteen days. In a given locality the epidemic commonly lasted for four to six weeks, allowing two to three weeks for it to reach its height and an equal period for its decline.

Meteorological Conditions.—Many of the older writers note the concurrence of surprising natural phenomena and outbreaks of influenza. We are left, however, with but one plausible relation—that of the seasons. Of 125 independent epidemics, collected by Hirsch, 50 began in the winter months, 35 in the spring months, 16 in the summer months, and 24 in the fall months. Once developed the disease seems to run its course equally through all the seasons. Its more frequent onset in the colder months may perhaps

PLATE XVIII

FIG. 1

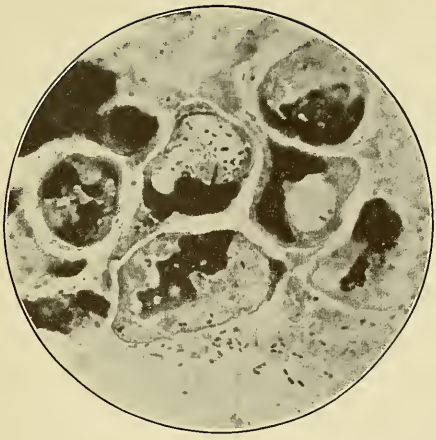


FIG. 2

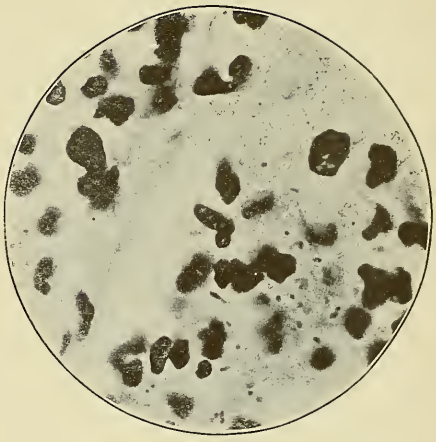


FIG. 3

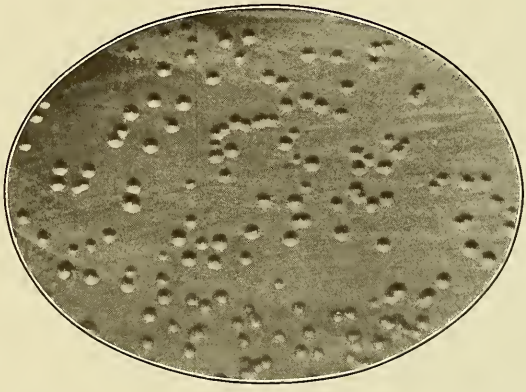


FIG. 4

FIG. 5

FIG. 1.—Influenza bacilli in sputum. × 1000.
FIG. 2.—Influenza bacilli in alveolar exudate. × 1000.
FIG. 3.—Culture of influenza bacilli on blood-agar (low magnification).
FIG. 4.—Smear preparation of influenza bacilli from culture. × 1000.
FIG. 5.—Smear preparation of influenza bacilli from culture, showing the occasional larger size of the organisms and their safety-pin appearance. × 1000.

be explained by a lack of sunshine, for Ruhemann finds that the number of cases of sporadic influenza is greatest when there is least sunshine.

Immunity.—Unfortunately we know little about immunity in influenza. Statistical studies of institutions on this point are rare, and it is to be hoped that in recurring epidemics more data will be obtained. In the Industrial School at Swinton in which 29 per cent. of the children suffered in 1890, it was noted that in the epidemic of the next year about twice as many cases occurred among those who had not previously had the disease.

Population immunity may explain the freedom of the European continent in the spring of 1891, while influenza was epidemic in the United States and the North of England. It may also account for the smaller proportion of persons attacked during the isolated epidemics which followed the pandemic and the gradual dying out of the disease in epidemic form. Variation in the virulence of the infecting organisms may likewise be a factor.

Influenza in Animals.—No definite relation has been established between epidemics in man and in animals.

Etiology.—In 1892, Pfeiffer[1] published his preliminary communication based on the study of 31 cases of influenza, with 6 autopsies. This was followed in 1893[2] by his more elaborate report on the etiology of the disease. The organisms were found in all the uncomplicated cases in pure culture in the sputum. He was unable to find them in many control investigations of ordinary bronchial catarrh, in pneumonia, or in phthisis, and they disappeared with the subsidence of the purulent secretion.

Methods of Examination.—*Staining*—The fresh sputum should be spread in a glass dish and the purulent masses or streaks separated by means of the platinum loop. In making cover-glass preparations great care should be taken to avoid contamination with the more fluid parts. The organisms take the stain with difficulty and therefore the staining fluid must be heated or allowed to remain on the cover-glass for five to ten minutes. The best results are perhaps obtained with Loeffler's alkaline methylene blue. Dilute carbol-fuchsin may also be used. When stained the organisms appear as minute rods, two to three times as long as broad, often in great numbers in and between the pus cells. Their ends are rounded and usually take the stain more deeply than the middle. They have no capsule and do not stain by Gram's method. In Smith's[3] method, the organisms stand out in strong contrast to the eosin coloration of the leukocytes.

Cultivation.—A purulent mass of sputum should be washed by two or more passages through sterile bouillon or salt solution. The organisms grow only in the presence of hæmoglobin, and culture tubes may be most conveniently prepared by pricking the previously sterilized dorsal aspect of the thumb, just above the nail, and smearing the blood on the surface of plain agar slants. The washed sputum is then transferred to the surface of this blood agar. After twenty-four to forty-eight hours in the incubator, if the culture is pure, minute, transparent, dew-drop like colonies appear, often visible only with a hand lens. They show little tendency to confluence. Under the microscope they are structureless. When growing in symbiosis with other organisms, the influenza colonies reach a much larger size, are more opaque, grayish-white in color, and show a fine granulation under the

[1] Pfeiffer, *Deut. med. Woch.*, 2, 1892, p. 28.
[2] Pfeiffer, *Zeit. s. Hygiene*, xiii, 1893.
[3] Smith, *Boston Medical and Surgical Journal*, December 18, 1902.

microscope. This peculiarity is most marked about colonies of *Staphylococcus pyogenes aureus*, a biological peculiarity first pointed out by Grassberger.

The influenza bacillus is strongly aërobic. No growth takes place above 43° or below 26° to 27° C. In sterile tap water at room temperature growth does not occur after thirty-two hours. On blood agar viability is lost, after fourteen to eighteen days, whether at room temperature or in the incubator. On repeated transplantation, however, especially in symbiosis with the staphylococcus, growth may be indefinitely prolonged. From dried sputum no growth can be obtained after thirty-six to forty hours. Spore formation has not been observed.

Pathogenesis.—Animals.—Pfeiffer was unable to cause a true infection in many experiments on mice, rats, guinea-pigs, rabbits, hogs, cats, dogs, and monkeys. Isolated examples of animal infection are found in the literature. The results are very inconstant and there is little evidence that multiplication of the injected organisms takes place. Jacobson reports an increase of virulence when injected with the streptococcus into mice. Slatineano, after serial passages with lactic acid through the guinea-pig, rabbit, and mouse, succeeded in killing animals with influenza bacilli alone.

Human Infection.—The microscopic picture of influenza pneumonia is so striking that the impression is irresistible that the bacilli crowding the leukocytes are the cause of the process. The finding of influenza bacilli as the sole infecting agent in extrapulmonary lesions affords valuable confirmatory evidence of its power for human infection. Pure cultures of influenza bacilli have been found in the pus of acute suppurative cholecystitis, in the exudate from a phlegmon of the arm, and in osteoperiostitis of the femur. They have also been demonstrated in a number of cases as the apparent sole cause of meningitis.

Agglutination.—Confirmation of the pathogenic power of the organism from the presence of a specific reaction has not yet been established. Cantani claims agglutination of influenza bacilli in normal salt solution mixed with the blood of influenza patients. In a series of such experiments, however, the writer found that the necessary dilution was low, that the reaction was very inconstant, and that the blood of apparently uninfected individuals also produced clumping.

Specificity.—The influenza bacillus, contrary to Pfeiffer's original observations, has been found in interepidemic periods, with or without influenza, by a great many investigators. It is not only a very frequent infecting agent in cases of acute respiratory disturbance during the interepidemic period, but may even be found in many cases of chronic cough, the origin of which in an acute attack cannot be established, as was shown in the writer's cases. In a series of 186 sputa,[1] from cases unselected except to exclude those with tubercle bacilli, organisms resembling influenza bacilli were found in 59 per cent. and in almost pure culture in 25 per cent. In 8 patients their constant presence in the sputum was demonstrated for two and one-half years, and the suspicion is strong that they had been present for a much longer period.

The most natural speculation seems to be that the great prevalence of influenza bacilli in interepidemic periods serves to bridge the gap between

[1] Lord, *Boston Medical and Surgical Journal*, May 11 and 18, 1905.

recurring outbreaks. Until proof can be offered to the contrary this must be assumed to be the explanation; but their relation with the disease rests only on their presence and more often in the severe cases with bronchitis and bronchopneumonia. They are frequently found in cases without a typical clinical picture of influenza, and the disease cannot be produced experimentally in animals. It may be that they are secondary invaders, and that the true cause is yet unknown. The solution of the problem may not be accomplished until the next pandemic and the necessary confirmation of Pfeiffer's belief in their etiological relation with the disease.

On the other hand the clinical and pathological picture caused by infection with other organisms cannot be differentiated from infection with influenza bacilli. The same symptoms of onset and course, a like degree of prostration, and similar pulmonary sequelæ, are common to them all. It may be, therefore, that other common respiratory organisms can set up epidemic as well as endemic infection. We must otherwise assume a different biological peculiarity for the influenza bacillus, enabling it alone to reach epidemic and pandemic prevalence, either through increase of susceptibility on the part of the host or increased virulence of the organism.

Classification.—Regarding the frequence of sporadic cases of influenza, it seems necessary to add to (1) pandemic influenza vera and (2) endemic-epidemic influenza vera, still another class, of (3) endemic influenza vera, also due to the influenza bacillus and serving to preserve the organisms for recurring outbreaks.

Pathology.—Because of the low mortality, observations on the pathology of the disease are not numerous. Our knowledge of this aspect is largely confined to changes occurring in the respiratory tract or its adnexa.

Swelling and injection of the nasal mucous membrane, with mucopurulent secretion, may be noted. Weichselbaum constantly found a purulent inflammation of the nasal sinuses. The frontal and ethmoid sinus and the antrum of Highmore may be invaded. Otitis media is frequent. Meningitis may occur. Inflammation of the larynx, trachea, and bronchi, may also be present.

In the lungs the typical change is bronchopneumonia, which may exist in isolated patches separated by air-holding tissue. The confluence of neighboring areas may resemble croupous pneumonia on superficial examination. On inspection, in the centres of the involved lobules grayish-yellow pin-head to pea-sized slightly elevated foci may be seen, surrounded by engorged pulmonary tissue. On pressure, a greenish-yellow thick pus may exude from the infiltrated tissue or the cut ends of the bronchi. On microscopic examination, the bronchial epithelium may be found lying free in the lumen, separated from the submucosa. The smaller bronchi may be entirely filled with leukocytes with complete absence of epithelium. The peribronchial connective tissue may likewise be infiltrated with cells. Enormous numbers may crowd the neighboring alveoli for varying distances from the affected bronchi and completely efface the normal pulmonary structure. The cellular character of the exudate is usually very striking, but varying amounts of desquamated epithelium, serum, and fibrin, are present. The fibrin, however, is much less abundant than in croupous pneumonia.

Great numbers of influenza bacilli are found in and among the pus cells of the bronchi and alveoli in the areas of most marked bronchopneumonia.

They become less numerous as the periphery of the lobular process is approached.

Abscesses.—In the microscopic sections of influenza pneumonia it is not infrequently noted that the alveolar septa are absent in small areas of most marked cellular infiltration, apparently forming the beginning of small abscesses. In a smaller number the cells in these places may be necrotic, suggesting the impossibility of full restoration to normal. Smith noted softening with abscess formation in sections from 1 of 5 cases. Well-marked pulmonary abscesses were present in 2 of 13 cases of influenza bronchopneumonia studied by the writer.

Induration.—In subacute or more chronic cases an increase of connective tissue can be observed. In Weichselbaum's study of 8 cases of bronchopneumonia in which he demonstrated influenza bacilli he observed a more or less advanced pulmonary induration in 3. In the writer's 13 cases pulmonary induration was present in 7 (macroscopic in 3, microscopic in 4).

The writer does not believe that the pathological picture of infection with influenza bacilli is distinctive. The same changes are seen in cases of bronchopneumonia representing infections with other organisms, in which influenza bacilli cannot be found.

Symptoms.—Incubation Period.—The interval between exposure and infection is undoubtedly short. In Parson's returns it was fixed usually at two to three days; in rare instances from a few hours to a week or more.

Typical Influenza Attack.—Prodromal symptoms are usually lacking. Most cases begin suddenly. An initial chill or chilliness is followed by fever, headache, and general pains. Malaise and prostration are usually striking. Catarrhal respiratory symptoms, commonly limited to the upper part of the tract, so frequently occur that they must be regarded as a part of the characteristic picture.

Disturbances referable to various organs may occupy the foreground, constituting the respiratory, nervous and gastric forms of the disease. In rare cases influenza may apparently occur as a simple fever, of short duration, without localization of the process. Various combinations of the different forms may appear in isolated cases, thus complicating the picture. The disease may present a different clinical picture at different times or in different places. Variations from the simple, uncomplicated type were more common in the succeeding epidemics than in that of 1889–90. In children the clinical picture may be even more variable, with a larger proportion of serious initial nervous phenomena. The duration of the simple and typical attack does not usually exceed one to several days. Convalescence is rapid in most cases but may be slow even after a mild infection.

Types of the Disease.—Despite its vagaries, the prevailing picture of the disease in all epidemics has been that of a respiratory infection. In Vogl's 278 cases from the last pandemic, the "overwhelming majority" had catarrhal symptoms in the nasopharynx, trachea, or bronchi. Eight were fatal from disease of the respiratory tract. The mortality returns from most of the large cities before, during, and after the epidemic, show that influenza has left its impression on them only in an increase of deaths from respiratory disease, which marks off with almost unfailing accuracy the prevalence of an epidemic in a given locality. A striking increase in the number of cases of inflammation of the middle ear during the epidemic still further fixes the respiratory tract as the place of election for influenza. It seems prob-

able, therefore, that respiratory infection represents the type of the disease. Symptoms arising in connection with other organs may be infection proceeding from an unrecognized portal of entry in the respiratory tract, or may be due to toxæmia. The local lesion may be slight and easily overlooked in the predominance of nervous, gastric, or febrile disturbances.

1. **Respiratory.**—The onset is like that in other acute diseases. The catarrhal process may begin at any part of the tract and remain localized, or spread by continuity. The upper air passages are more frequently involved. Prostration is often strikingly out of proportion to the local lesion. In mild cases the symptoms may rapidly subside. In more severe attacks the secretion is abundant and the whole tract may become involved. The fever continues; there may be delirium and great weakness. With invasion of the deeper parts, cough may be very distressing, with dyspnœa and cyanosis.

Rhinitis.—Coryza is perhaps the most common symptom. It may be accompanied by anosmia and conjunctivitis. Extension of the inflammation to the ethmoid cells, the frontal or sphenoidal sinus, and the antrum of Highmore, is common in severe infection. Distressing frontal headache or facial neuralgia may result. Influenza bacilli, mixed with other organisms, have been demonstrated in all these regions.

Tonsillitis.—Rawness of the throat, with redness of the tonsils and slight enlargement of the cervical glands, is common. The general symptoms may be severe, but marked local changes are rare. Tonsillitis was reported in only 3 per cent. of the 287 Bavarian army cases. Influenza bacilli are usually mixed with others in tonsillar infection, and in some instances the process may apparently be mistaken for diphtheria. Jehle regards the tonsils as the portal of entry for infection of the blood, finding influenza bacilli in their parenchyma and not elsewhere in the respiratory tract in 3 of 7 cases of septicæmia.

Laryngitis.—Laryngitis may occur; at times the infection is severe, with fever, hoarseness, aphonia, and dyspnœa. Œdema of the glottis has occurred in rare instances. Tracheitis is frequently present and may be accompanied by substernal tickling and a burning sensation.

Bronchitis.—Bronchitis usually results by extension from above, and is a very important manifestation. The cough is at first dry and the sputum scanty. If the finer bronchi are invaded the cough is more distressing and may be paroxysmal. Dyspnœa may be a troublesome feature and cyanosis may be marked. The temperature is usually elevated, falling to normal in favorable cases within a week. If only the larger tubes are involved there may be no objective signs of the disease. It is more common, however, to find rales throughout the lungs and more marked at the bases. They may be localized at the apices, and the subacute or more chronic cases are not infrequently mistaken for tuberculosis. When localized rales persist at one or more places, bronchopneumonia should be suspected.

The sputum becomes more abundant after a few days and contains greenish-yellow purulent masses. The character of the sputum is not distinctive of infection with influenza bacilli. In the more severe cases the cough and expectoration usually continue with gradually diminishing severity for six to eight weeks. Though the excretion from the upper parts of the respiratory tract usually shows a mixture of various organisms, that from the bronchi and lung at first often contains a pure culture of influenza bacilli; but as the process clears up and the amount of sputum diminishes, other organisms are likely to appear.

Bronchopneumonia.—This is one of the most important manifestations. Its frequence is difficult to estimate and it is probably more common than statistics show, not only because of the readiness with which small patches may be overlooked, but also from the failure of many observers to class pneumonia as a manifestation of influenza. In practically all series of cases, both lobar and bronchopneumonia are included. Of the 55,263 German army cases, 534 (0.97 per cent.) had pneumonia. F. C. Shattuck found 8 cases (less than 0.5 per cent.) among 1,699 patients with influenza at the Pacific Mills.

The lungs are usually invaded by extension from the bronchi, but may apparently be primarily involved. When preceded by bronchitis the pneumonia seldom begins until after the fourth day. Its onset may be indicated only by an increase of the existing symptoms. It is rarely abrupt and the initial chill is uncommon. The pleural pain of croupous pneumonia is often absent. There is increase of the dyspnœa and the sputum is at times blood-tinged; but the rusty sputum of croupous pneumonia is not seen in uncomplicated bronchopneumonia. The expectoration is often made up of discrete greenish-yellow masses surrounded by mucus. Similar sputum is seen in pulmonary tuberculosis and after infection with other organisms than the influenza bacillus. Influenza bacilli can often be obtained in pure culture from the well-washed purulent masses.

The temperature may be only slightly elevated, is often irregular, and usually terminates by lysis after a variable period. In severe cases it may remain elevated for weeks. Sweating is frequently noted. Solidification may occur at any part of the lung. The foci may be multiple or confined to a single area no larger than the bell of the stethoscope. The lower lobes are more frequently affected.

The diagnosis of influenza pneumonia is often difficult or impossible, unsuspected consolidation being found at autopsy. Objective signs may be limited to persistent rales at one or more places. Bronchial breathing may be present without dulness, if the solidification is central. In more superficial processes, there is bronchial breathing with dulness, increased vocal and tactile fremitus, but the signs are likely to be more atypical than in lobar pneumonia. They may simulate fluid, and exploratory puncture should not be delayed.

Signs of pulmonary solidification often outlast the rise of temperature. Resolution may be very slow and yet finally end in symptomatic efficiency of the lung. In one case of influenza pneumonia followed by the writer, the bronchial breathing disappeared only after six months, and there are now no signs of disturbance.

Abscess and Gangrene.—Though complete resolution may follow influenza pneumonia, it is very common in fatal cases to note small losses of pulmonary substance. This is probably not peculiar to infection with influenza bacilli but may be found in a large proportion of cases of bronchopneumonia due to other organisms and in which influenza bacilli cannot be demonstrated. The necrotic foci are usually small and may be suspected during life only by signs of localized bronchitis. By extension or the fusion of neighboring areas, larger losses of substance may occur. Among Fraenkel's 80 cases of influenza pneumonia there were 6 of pulmonary gangrene. The sputum is foul and contains elastic fibers. Influenza bacilli are usually mixed with various other organisms but Hitzig has reported a case of pneumonia

followed by abscess formation in which he demonstrated pure cultures of influenza bacilli eight times during a period of five weeks. When the lung is extensively involved with an increasing amount of sputum and continued fever the case assumes a serious aspect. Every effort should be made to localize the process. The *x*-rays are a valuable adjunct to physical examination, and the involvement of the overlying pleura may indicate the site. In more favorable cases the abscess is walled off and the patient left with a cavity communicating with the neighboring bronchus, which may be dilated. The affected lung may contain numerous cavities. Pulmonary induration usually accompanies these changes.

Chronic Influenza.—It is not surprising that the acute attack should occasionally initiate a chronic cough. The losses of pulmonary tissue serve as permanent pockets for influenza bacilli. The writer has seen 3 cases in which influenza bacilli persist in the abundant purulent sputum two and one-half years after the acute attack. Leichtenstern followed 2 patients from the acute attack to their death two years later. No tuberculosis was found at autopsy.

Chronic infection with influenza bacilli is a very frequent clinical finding. Eighteen such cases were reported by the writer in 1902. It is often impossible to establish the onset in an acute infection, and the process seems to have begun insidiously. Perhaps the most surprising feature is the continued presence of the organisms in a condition of practical purity in the well-washed sputum, as was shown in 8 of these cases for a period of two and one-half years.

The cases may show only local or diffuse bronchitis on physical examination, yet some damage to the pulmonary tissue has probably always occurred. In other cases slight dulness or broncho-vesicular breathing may establish the site of the pulmonary process. In the more severe cases the symptoms are those of local or diffuse bronchiectasis. The sputum may reach an enormous quantity, sometimes amounting to a pint or more in twenty-four hours. Blood streaks or even frank hæmoptysis may be present without tubercle bacilli in the sputum or a reaction to tuberculin. Such hemorrhages come from abscess cavities or congested veins in the walls of dilated bronchi. The cases closely simulate tuberculosis, but their course is more favorable. They do not tend toward a fatal termination, but rather remain stationary or slowly advance, unless acute bronchopneumonia arises from the chronic infection, or death results from some intercurrent disease. In one case the cough had lasted for forty-four years, and death followed cerebral hemorrhage. At autopsy, bronchiectasis, chronic interstitial pneumonia, and abscess formation have been found.

Pneumothorax and Empyema.—If abscesses are present at the periphery of the lung, their rupture may lead to invasion of the pleural sac, resulting in fibrinous pleuritis, pneumothorax, or empyema. The exudate may contain pure cultures of influenza bacilli, but mixed infections are more common. Empyema was present in 6 of Mason's 77 cases of influenza pneumonia.

Lobar Pneumonia and Influenza.—Many writers think that lobar as well as bronchopneumonia should be regarded as a manifestation of influenza. It does not seem that any convincing arguments as yet support this view. Bronchopneumonia is far more common than lobar pneumonia in influenza; but in some cases the two forms may co-exist as is shown by autopsy. The pneumococcus is the usual cause of lobar pneumonia and has

never been shown to bear any definite relation to influenza. In uncomplicated cases, lobar pneumonia runs a clinical course and presents anatomical features quite different from the bronchopneumonia of influenza. The writer has repeatedly sought influenza bacilli in the exudate of lobar pneumonia, and in typical cases has never demonstrated them in stained sections. It is not surprising that croupous pneumonia should occur in a small number of cases of influenza, from the almost constant presence of pneumococci in the air passages. The respiratory disturbances accompanying influenza may readily favor their multiplication and determine their invasion of the lung. The clinical distinction between the two forms may be impossible, and the croupous pneumonia complicating influenza may run a very atypical course. The evidence seems to point to it rather as a complication than as a manifestation of the disease.

Relapse.—Some patients who have once suffered from influenza seem to be especially liable to recurrences; which may be due to the persistence of the bacilli, undetected, in the upper parts of the respiratory tract, causing auto-reinfection. We know that they may persist for years in some cases. Relapse is more frequent in the colder months of the year, but may immediately follow the original attack after some indiscretion, especially exposure to cold. It is usually less severe than the first infection.

2. **Nervous.**—It has been said that the clinical picture of influenza is incomplete without nervous phenomena. This is probably true, in previously uninfected individuals, if we include the minor nervous disturbances. Headache and general pains are seldom absent in acute cases. Prostration is frequent and often far outlasts the symptoms of the disease. Vertigo, insomnia, even delirium and coma, may occasionally be observed. The nervous symptoms may so far predominate that local respiratory changes are overlooked. In some cases, to judge from the literature, nervous disturbances may be the only manifestation. In such cases, however, it is difficult to exclude diseases which have no relation with influenza.

Aside from the initial nervous symptoms, neuralgic pain is one of the most common disturbances. It usually occurs after the decline of the fever and may last long into convalescence. Hardly a nerve in the body has escaped a relation with influenza. The supra-occipital, the intercostal, and the sciatic nerves, are most frequently affected. Among the German army cases persistent nerve pain was noted in 254 (0.46 per cent.). Myalgia, joint pains, hyperæsthesia, and anæsthesia, may accompany the attack. Neurasthenia may be initiated, but such cases have usually had previous symptoms.

Various other nervous disturbances may accompany or follow influenza. Their relation with the disease is somewhat uncertain because of their rarity. Thus peripheral neuritis may follow influenza as it follows other infectious diseases. Cases may even assume the type of Landry's paralysis. The prognosis may be considered better than after diphtheria. The localized forms may be of central origin. Paralysis of various muscles of the eye, alone or combined with the palatal or pharyngeal muscles, has been said to occur, but such cases may have been due to unsuspected diphtheria. Affections of the spinal cord are less common, but hemorrhagic myelitis and acute anterior poliomyelitis may be observed. Epilepsy has immediately followed influenza. Two such cases were observed in the German army.

Psychoses may follow influenza as they do typhoid fever or ordinary pneumonia. An inherited or psychopathic disposition can often be demon-

strated. The prognosis is favorable in cases dependent on influenza and without predisposition to the disease. Patients have been admitted to insane asylums and discharged well after a few weeks, but more severe cases may not recover for months.

Encephalitis may arise apparently by extension from the middle ears, the nasal or frontal sinuses, and the antrum of Highmore; from metastasis in pulmonary abscess, empyema, or purulent bronchitis; or it may be impossible to find a primary source. The cerebral lesions are multiple or single, and hemorrhage may be a striking feature on examination of the involved area. Monoplegia, hemiplegia, coma, convulsions, or delirium, may result. Leichtenstern was the first to describes such cases, and Pfuhl claims to have found influenza bacilli in cerebral tissue; but his bacteriological work is defective and his results can not be accepted without question.

Meningitis.—Though this must be regarded as a very rare manifestation of influenza, occurring in only 4 of the German army cases, it is of special interest because of the finding of influenza bacilli in the exudate by several observers. Toxæmia has been said at times to simulate meningitis, but it must always be a question without lumbar puncture whether a true infection has not been present and followed a very favorable course.

There are 7 cases of meningitis recorded in the literature in which pure cultures of influenza bacilli have been found and in which the identification of the organism was complete (cases of Nauwerck, Fraenkel, Slawyk, Meunier, Langer, Ghon). There are 4 more cases (cases of Hoegerstedt, Haedke, Peucker, Hecht) in which the reports are trustworthy, but in which influenza bacilli were mixed with other organisms in the meningeal exudate. Thus in all there are at least 11 cases in which influenza bacilli have been found. The organisms have been obtained by lumbar puncture, during life, by four observers (cases of Slawyk, Meunier, Trailescun, Hecht). It is not possible to obtain data from all the reports concerning the origin of the process, but the meningitis seemed to arise by extension from otitis media in one (Haedke), from empyæma of the antrum of Highmore in a second (Ghon), and by metastasis from influenza pneumonia in three (Ghon, Peucker, Hecht). In one case (Slawyk) the meningitis seemed to be part of a general infection with influenza bacilli.

The cases closely resemble meningitis due to the pneumococcus or meningococcus. Their influenzal origin may be suspected during an epidemic or when some primary focus of influenza can be demonstrated. Even then, without lumbar puncture, their bacterial cause remains uncertain. From their more sudden onset and more rapid course the clinical distinction between influenza and tuberculous meningitis can often be made.

The pathological picture of influenza meningitis is not characteristic. Fraenkel was unable to distinguish pneumococcus, meningococcus, or influenza bacillus meningitis, either micro- or macroscopically.

The prognosis is not always unfavorable. Langer's case was a child aged nine years who had been sick for eight days with headache, vomiting, and stiff neck. The temperature dropped and there was almost immediate subsidence of symptoms after lumbar puncture. The patient was discharged well on the twentieth day.

3 **Gastro-intestinal.**—This form of influenza as an entity is of uncertain existence. The symptoms referred to this tract may be toxic phenomena from the respiratory or nervous form of the disease. On the other hand, in

the German Collective Investigation 39 cards deal with this point and only 1 denies the possibility of separating the different forms, while 38 affirm the distinction. It is to be hoped that in recurring epidemics the specific cause of the disease will be demonstrated in the lesions or that cases with exclusive gastro-intestinal symptoms, will be shown to be more frequent than before or after the epidemic period Until this can be done we must rely on the impression of medical men for the establishment of the group. The writer has never seen a case with absence of respiratory symptoms in which the diagnosis was sure.

In cases with predominance of gastro-intestinal symptoms, the tongue may be coated, vomiting marked, and the abdomen tender on pressure. Constipation is more common than diarrhœa, which, however, may be severe in some cases. Intestinal bleeding has been described. Hyperæmia, ulceration of the stomach and intestines, appendicitis, and peritonitis, have been associated with influenza. Though it is probable that influenza bacilli may set up catarrhal processes in the tract, secondary to the respiratory invasion, as yet there are no trustworthy observations on their presence here. Heyrooski obtained a pure culture of influenza bacilli from the pus of a case of cholecystitis and cholelithiasis. The identification of the organism was complete. Fisch and Hill cultivated influenza bacilli from the peritoneal pus of a fulminating case of peritonitis. Similar organisms were also found in the bronchial secretion and the spleen. No intestinal lesions were found. The cultures are not carefully described.

4. **Typhoid Form of Influenza.**—Cases with fever, headache, delirium, meteorism, and diarrhœa, may at first suggest typhoid fever. Rose spots have even been described in influenza. A palpable spleen has been noted in as high as 12 per cent. of cases of influenza by Schultz, while it occurred in only 4.7 per cent. of Krehl's cases. It may be that continued fever with only transient local manifestations may follow infection with influenza bacilli; but the more acute onset and shorter course may serve to differentiate the two diseases. The writer has frequently found influenza bacilli in the sputum of patients with continued fever who gave positive Widal reactions, showing that the two infections may co-exist; and it is not certain that the so-called typhoid form of influenza is not unrecognized typhoid fever.

5. **Metamorphosing Form of Influenza.**—Leichtenstern mentions an occasional sudden change in the clinical picture. At the beginning, gastro-intestinal symptoms may be exclusively present, followed a few days later by a sudden transition to the respiratory type, with diffuse bronchitis and coincident recession of the gastro-intestinal disturbances

Jaundice probably bears only a chance relation with influenza, being noted in only 2 of 439 cases by Leichtenstern.

Parotitis has been occasionally observed as in other infectious diseases. It occurred in 12 of the German army cases.

6. **Circulatory System.**—Functional cardiac disturbances are not uncommon in influenza, but are not distinctive and are such as may occur in any acute infectious disease. The pulse rate is usually elevated in proportion to the fever, but in some cases tachycardia may be noted. Bradycardia, palpitation, irregularity, and dicrotic pulse, may be occasionally seen.

Endocarditis.—Influenza is so seldom followed by permanent cardiac disturbances that it is not usually held responsible for valvular disease. It seems probable, however, that it is not as blameless as is commonly be-

lieved. More recent observations on the bacteriology of the disease show that influenza bacilli not infrequently invade the blood stream, especially in severe attacks. Their lodgment on the cardiac valves has been established by Jehle, who cultivated them from acute aortic endocarditis in 2 cases; in 1 they were in pure culture, in the second mixed with staphylococci. Pericarditis may arise by extension when the lung or pleura have become involved. Influenza bacilli, mixed with other organisms, have been found in the exudate.

Disturbance in the peripheral vessels—phlebitis, venous and arterial thrombosis—may occur, as might be expected from the infectious nature of the disease.

Septicæmia.—Numerous observers have described organisms resembling influenza bacilli in the blood of patients with influenza. The identification of these bacteria, however, has usually been solely on their morphology and without the confirmation of cultures. Blood cultures and the search for influenza bacilli should be more systematically made in acute febrile infections of obscure origin. Thus far the only trustworthy data concern their presence in the blood as terminal infections. Meunier[1] cultivated them from the blood before death in 4 of 8 cases of bronchopneumonia in children. They have been found in the heart's blood after death by Rosenthal, Doering, and Jehle. Jehle's work is of especial interest. His observations were all at the postmortem table. Of 20 cases with pulmonary influenza the bacilli were found in the blood in only 3. In the acute exanthemata, on the contrary, an invasion of the blood by influenza bacilli was almost the rule. Cultures were made from 29 cases of scarlet fever, in which they were found in 22. In 15 of these positive cases, pulmonary influenza was also present. In the remaining 7 cases the bacilli could not be found in the respiratory tract proper, but in 3 they were present in the tonsils, which he regards as the probable portal of entry. Of 18 cases of measles, influenza bacilli were found in the blood in 13; of 9 cases of varicella, in 5; of 24 cases of whooping-cough, in 2; of 9 cases of diphtheria, in 1. Slawyk has reported an apparent general infection with influenza bacilli, which he found in the cerebrospinal fluid, in the blood from the finger, and in a superficial abscess on the back of the hand. Similar bacilli were found after death in fluid from the ventricles of the brain and in sections of the lung.

The Blood in Influenza.—In 7 cases of influenza, with symptoms referable to the respiratory tract, Rieder found from 2,800 to 6,700 leukocytes per cubic millimeter. In 5 cases of influenza pneumonia they numbered 8,200 to 13,800. In 5 cases of doubtful influenza pneumonia, the white count varied from 4,600 to 20,100. In 10 cases of lobar pneumonia, on the other hand, he found a constant leukocytosis.

We have made leukocyte counts on 233 cases of influenza at the Massachusetts General Hospital. Of these 167[2] represent the simple and typical

[1] Meunier, *Arch. gén. de méd.*, February and March, 1897.

[2]

Between	2,000	and	4,000	4	
"	4,000	"	8,000	44	
"	8,000	"	12,000	68	
"	12,000	"	16,000	30	(2 with otitis media).
"	16,000	"	20,000	16	(1 with otitis media).
"	20,000	"	24,000	3	
"	26,000	"	35,000	2	
				167	

form of the disease, with an acute onset, usually with fever of short duration, and in most cases slight respiratory disturbance. The leukocytes do not exceed 12,000 in about 70 per cent. The leukocytosis in the remaining cases cannot be accounted for by the presence of complications, nor is there any relation between the white count and the severity of the infection. With the involvement of the deeper part of the respiratory tract the proportion of cases with leukocytosis increases as only about one-half of 54 cases[1] with bronchitis, and only one-third of 12 cases[2] with pneumonia show 12,000 leukocytes or under.

7. **Genito-urinary.**—Beyond the slight disturbance in the kidney commonly found in any acute infectious disease, there is nothing particularly noteworthy in influenza, which seems to spare this organ in the vast majority of cases. In very rare instances a nephritis has been noted, as in 10 of the German army cases. The finding of influenza bacilli in the kidney at autopsy has been reported by Paltauf and Kretz, and J H. Wright demonstrated them in a case of pyonephritis. Cystitis and orchitis have been described. Abortion following an attack of influenza has been frequently noted, especially by the older writers.

8. **Skin.**—Herpes of the lips and nose may be seen in a small proportion of cases. It was noted in 5 per cent. of Leichtenstern's 105 cases of pneumonia and in 3 per cent. of 334 uncomplicated cases. Erythema, scarlatinal, measly, and other exanthems, have been ascribed to influenza; but they are not distinctive and occur so infrequently as to suggest drug rash or a confusion with other diseases.

9. **Joints.**—No special relation has been established between arthritis and influenza. Though as yet there are no publications on influenza bacilli in the joints, a systematic search would probably disclose their occasional presence. "Acute articular rheumatism" was observed in 44 of the German army cases.

10. **Special Senses.**—*Ear* —The relation between influenza and inflammation of the middle ear is undoubted. Though otitis media was noted in only a small proportion of the series of cases reported from the last pandemic, slight catarrhal inflammation is common and it was generally observed by ear specialists during the outbreak that the number of cases seeking admission far exceeded those before and after the epidemic. Gruber,[3] for example, saw 324 cases of otitis media (138 catarrhal—186 puru-

[1] Between 2,000 and 4,000 ... 2
" 4,000 " 8,000 ... 8
" 8,000 " 12,000 ... 18
" 12,000 " 16,000 ... 15
" 16,000 " 20,000 ... 6
" 20,000 " 24,000 ... 3
" 24,000 " 28,000 ... 2
54

[2] In 12 uncomplicated cases of influenza pneumonia, the white count was:—
Between 5,000 and 6,000 ... 3 (2 fatal).
" 11,000 " 12,000 ... 1
" 13,000 " 17,000 ... 3 (1 fatal)
" 20,000 " 30,000 ... 3 (1 fatal).
Over 30,000 ... 2
12

[3] Gruber, *Wiener med. Woch.*, No. 10, 1890.

lent) during the month of January, 1890, while his monthly average for January at other times was 58 cases.

Extension of the catarrhal process through the Eustachian tube may arise during the acute stage or in convalescence. The clinical character of the cases lacks distinctive features. Involvement of the mastoid and invasion of the meninges may occur. Otitis media should always be suspected in children with severe obscure symptoms. Perforation of the membrana tympani may be the first objective sign. Influenza bacilli have been frequently demonstrated in the middle ear, but usually mixed with other bacteria.

Eye.—Conjunctivitis may be noted in a variable proportion of cases. It was observed in as high as 40 per cent. of Stinzing's 405 patients.[1] The process is usually benign, and no marked increase of the number of those seeking admission to the eye clinic was noted during the epidemic. In the more severe cases the conjunctivitis is accompanied by photophobia and œdema of the lids. The bulbar conjunctiva may be involved and corneal ulceration may result. Iritis and iridocyclitis have been described. Influenza bacilli have been found in the conjunctival secretion. In the fall of 1904 the writer cultivated them from a patient with conjunctivitis sent to the Massachusetts General Hospital by F. M. Spalding. Rymowitch believes that the influenza and Koch-Weeks bacillus are identical, the two organisms presenting the same morphological, cultural, and pathogenic characters.

Influenza and Other Diseases.—Though it has often been thought that during epidemics of influenza other diseases do not prevail to the same extent, the reports are conflicting, and it may be that during the outbreak of influenza other diseases are at times wrongly included under its manifestations. The unfavorable influence of influenza on existing disease, however, is undoubted. Superimposed on phthisis, emphysema, cardiac disease, nephritis, or diabetes, it may lead to a fatal termination. Jehle found that during a small local outbreak both the morbidity and mortality of scarlet fever was increased.

Phthisis.—The effect of influenza on phthisis is difficult to estimate in isolated cases, but is shown by hospital and mortality statistics. Sixty-seven cases were discharged because of phthisis, from service in the garrison in Munich during the year preceding the 30th of September, 1889; but within the next six months, during the epidemic of influenza, 132 cases were discovered. The diagnosis was based on the finding of tubercle bacilli in the sputum. The vital statistics for Paris show that 349 persons were reported as having died from phthisis between December 22, 1888, and January 4, 1889, while 886 deaths are recorded from the same cause during an equal period in 1889–90. Following the epidemic it was observed that the number of deaths from tuberculosis fell below normal, suggesting that influenza had merely hastened the fatal termination. In some cases influenza pneumonia may complicate phthisis without apparently exerting an unfavorable influence.

Diagnosis.—**Clinical.**—During epidemics and pandemics this presents little difficulty in cases beginning suddenly with chills, fever of short duration, headache, general pain, loss of appetite, and prostration out of proportion

[1] Stinzing, *Münch. med. Woch.*, No. 93, 1890.

to the other symptoms. The patient may complain of no local lesion, but catarrhal disturbances are almost the rule. They may be transient and easily overlooked in the predominance of nervous and gastro-intestinal symptoms. The protean character of the disease makes it difficult to separate its rarer manifestations from diseases of a different etiology occurring during epidemics.

Bacteriological.—Influenza bacilli can be recognized after some practice from their morphology and staining reaction alone in most cases. To be certain of their identity, however, they must be cultivated. As yet no proof has been offered that Pfeiffer's "Pseudo-influenza bacillus," the whooping-cough bacillus, Jundell's Bacillus catarrhalis, Müller's trachoma bacillus, and the Koch-Weeks bacillus, are not identical with the true influenza bacillus.

Other Catarrhal Respiratory Infections.—In the interepidemic period it does not seem that the respiratory infection with influenza bacilli can be distinguished from infections with other organisms, such, for example, as the Micrococcus catarrhalis, without a bacteriological examination of the sputum. In the clinical picture, symptoms of onset, the course and duration of the different infections, there seems to be nothing distinctive. The amount of prostration may be as great in one as in the other. The pathological picture in cases of bronchopneumonia, due to the different organisms, likewise seems to be similar in the character of the exudate, its varying extent and intensity, and the tendency in a small proportion of cases to end in permanent damage to the pulmonary tissue.

Tuberculosis.—Infection of the lungs with influenza bacilli may closely simulate pulmonary tuberculosis. The persistence of rales at some place in the lung may be due to small losses of substance during an undetected influenza bronchopneumonia. Signs of cavity or long-continued pulmonary solidification may result from infection with other organisms than the tubercle bacillus. It is by no means rare to see patients in whom the suspicion is strong that the disease is pulmonary tuberculosis, from the long-continued cough, occasional attacks of hæmoptysis, and suspicious physical signs; but repeated examination of the sputum fails to reveal tubercle bacilli and no reaction is obtained after the injection of tuberculin. The writer has reported 8 cases[1] from the Massachusetts General Hospital in which the confusion might readily have occurred or in which the clinical diagnosis of pulmonary tuberculosis had been made, but without tuberculosis at autopsy. If a history of preceding catarrhal symptoms or an onset with an acute febrile attack can be obtained, influenza should be suspected. Hæmoptysis occurring without catarrhal symptoms is likely to be due to tuberculosis; but in the presence of serious damage to the pulmonary tissue it may come from abscess cavities of a non-tuberculous origin.

The early detection of pulmonary tuberculosis is so important that it is usually safer to give the patient the benefit of the doubt and treat him for tuberculosis; but in view of the impossibility of making the diagnosis without finding tubercle bacilli in the sputum, their presence should be regarded as the only infallible indication of this condition. As only about one-half of the cases reported as cured in the statistics of institutions for the cure of tuberculosis are thus proved, it is probable that non-tuberculous cases are included and the percentage of reported cures thus materially raised. In their

[1] Lord, loc. cit.

clinical course these cases are more favorable than tuberculosis, tending rather to remain stationary or slowly advance, unless fatal from some intercurrent disease.

Dengue.—Influenza has been frequently confused with dengue, which, however, is confined to tropical or subtropical regions and occurs more often during the warm months of the year. Its spread from place to place is slow compared with influenza. It prevails as an epidemic in a given locality for from two to five months, while influenza is usually over within six to eight weeks. Unlike influenza, it commonly leaves no impression on mortality statistics in an increase of deaths from disease of the respiratory tract. Catarrhal symptoms are lacking; diseases of the lungs or nervous system are almost never present. Herpes is not seen in dengue. Arthritic symptoms, especially of the knee joints, total anorexia, and a thickly coated tongue, are common. A transient, measly, scarlatinal, or erysipelas-like eruption, with desquamation and often persistent pruritus, is pathognomonic. Unlike influenza, ambulant cases are rare, and the convalescence is usually protracted.

Typhoid Fever.—The milder cases of this may offer some difficulty. The onset in typhoid fever is usually less abrupt, but catarrhal symptoms are frequent. In some cases the diagnosis cannot be made during the first few days. Continued fever, rose spots, and enlargement of the spleen, will usually serve to distinguish the true condition. Blood cultures, the finding of typhoid bacilli in the rose spots or stools, and the Widal reaction, may settle the diagnosis.

Prognosis.—Few die compared with the number who are attacked. Many statistics are untrustworthy because some of the more serious manifestations are not included. Influenza becomes more dangerous with advancing years or in patients with phthisis, cardiac disease, emphysema, diabetes, etc. Of the 55,263 German army cases, only 59 died from influenza—42 with pulmonary symptoms. Of 22,972 cases in Munich, death was ascribed to influenza in 133, of whom 69 died of pulmonary disturbance. The influence of age is apparent in these cases, 88 being between fifty-one and ninety. Influenza pneumonia is more serious than lobar pneumonia. Various estimates place the mortality at from 17 to 50 per cent. It is to be feared not only from its high mortality, but also because of its distressing sequelæ, arising from occasional permanent damage to the pulmonary substance. Continued cough, recurring respiratory infection, chronic bronchitis, emphysema, pulmonary induration, and bronchiectasis, add to the seriousness of this manifestation of the disease. Meningitis is not always fatal, as is shown by the recovery of Langer's case after lumbar puncture.

Prophylaxis —The contagious nature of influenza seems to have been conclusively proved. The secretion from the respiratory tract must be regarded as the principal source of contagion. It is improbable that the influenza bacillus multiplies under any ordinary conditions outside the human body. To judge from laboratory experiments its infective power is probably soon lost in dried sputum. The enormous numbers in which it exists in the secretions perhaps overbalances the rapid death of the organism. Contact infection and the drying of sputum should be guarded against.

The most important preventive measures concern the elimination of recurring epidemics. If the influenza bacillus is the cause it maintains its existence by numberless interepidemic infections and by its persistence for

years in the respiratory tract of individuals with chronic cough. In unselected cases the writer has found the organism present in from 25 to 59 per cent. of all cases with cough and expectoration in an interepidemic period. If we are to prevent the recurrence of widespread outbreaks of the disease, it is to these cases of acute and chronic respiratory infection occurring outside of epidemics that our preventive measures must be directed. The same control should be exercised over all cases of respiratory infection as is now being attempted for tuberculosis in most of the large cities. Influenza should be considered as constant a danger as tuberculosis, though its manifestations are less serious. All patients with cough and expectoration coming to polyclinics or seen in private practice should be warned against the danger of transferring infectious material from person to person, with the same care that is recommended for tuberculosis.

During epidemics persons at the extremes of age should be protected with especial care. When possible isolation should be practiced. Infected boats should not land passengers at uninfected ports. Mass meetings should be discouraged. Infected children should be kept from school.

Tuberculous patients should be guarded at all times from influenza infection. On the other hand the admission of unproved cases to institutions for the cure of tuberculosis subjects them to an unnecessary danger. If they are admitted on suspicion of tuberculosis they should be placed in separate wards until they can be proved to be tuberculous by the finding of tubercle bacilli in the sputum. The damaged condition of their bronchi and lungs renders them more susceptible to the tubercle bacillus, which has been shown by Cornet and others to abound in the dust of closed places where tuberculous patients are confined. Hospital cleanliness does much to minimize this danger, but it does not entirely eliminate it, and the occasional infection of the attendants in even the most carefully kept institutions confirms this.

Every infected individual should understand that his sputum is a danger to others, and if allowed to dry may be capable of spreading the disease. It should be expectorated carefully, into a special receptacle, to avoid soiling the beard or moustache. In coughing or sneezing, expelled particles of sputum should be caught in a piece of cloth placed in front of the mouth. These are to be burned. The fingers should not be moistened in the mouth in turning the leaves of books, public documents, etc. Soiled bed- and body-linen should be boiled for one-half hour before it is sent to the laundry. Patients' thermometers and table utensils should be kept separate, the latter boiled after use. Dusting the rooms of influenza patients should be done with a damp cloth; sweeping, with a dampened broom. An infected individual should sleep alone. Sunlight and fresh air limit the danger.

The safest method of disposal of sputum is cremation. The most efficient of the ordinary disinfectant solutions is probably carbolic acid (5 per cent.), which may be left in contact with the sputum for twenty-four hours.

Patients who continually harbor the influenza bacillus in some part of the respiratory tract should be especially careful to avoid exposure to wet and cold. Catarrhal symptoms so frequently follow such indiscretion that something more than a chance relation must exist between exposure and acute respiratory infection or reinfection. The experiments of Rossbach and Müller on animals have shown that the chilling of the body is followed by a

transitory increase of bronchial secretion, which may serve as a favorable medium for the multiplication of organisms in an already infected tract. Some protection may be afforded by thin woolen underwear and efforts at increasing individual resistance;—sleeping with the window open, spending much time in the open air, and cool morning baths followed by friction. A good reaction should be secured after the bath. The hardening process should not be begun during cold weather.

Treatment.—There is no specific for influenza. In the great majority of cases the disease runs its course independent of treatment. The diet should be regulated and should be light and easily digestible in cases with gastro-intestinal symptoms. With involvement of the respiratory and nervous systems there are no special restrictions, and the patient may take as much food as can be easily digested.

Even the mild cases should be regarded as serious, and the patient confined to the house and the bed, remaining there until the acute symptoms and fever have subsided. At the onset the patient may take a hot bath and be put to bed between warmed blankets with hot water bottles at the feet. A drink of hot lemonade may serve to start perspiration, which is often followed by surprising relief of the headache and general pains. An increase of respiratory symptoms may follow the chilling of the body, and cold should be limited to local applications for pain.

If the headache and general pains are distressing an ice-cap and Dover's powder gr. 10 (0.65 gm.) may be ordered. If the bowels have not moved, a mild saline cathartic, as sodium phosphate, 30 gr. (2 gm.) in half a tumbler of lukewarm water may be given. The coal-tar products must be used with caution, but if the headache, general pains, hyperæsthesia, or insomnia, are marked, antipyrine or phenacetine, gr. 10 (0.65 gm.), with caffeine gr. 3 (0.20 gm.), may give evident relief. They are of service also in the severe neuralgic pains following influenza. Their use must not be long continued. When facial neuralgia persists, disease of the nasal sinuses should be suspected. The bromides, nitroglycerine, salicylic acid, salipyrin, etc., may be given a trial. Locally, chloral and camphor, chloroform liniment, menthol, etc., may be of service. In lumbago, sacro-iliac disease should be suspected. In sciatica a rectal examination should not be omitted. The thermocautery, or electricity, may be tried.

If the patient is harassed by irritative attacks of cough, heroin gr. $\frac{1}{12}$ (0.005 gm.) or morphia should be used. If the secretion is raised with difficulty ammonium chloride gr. 10 (0.65 gm.) often seems to be of great service. If the cough persists tubercle bacilli should be repeatedly looked for in the sputum. Unless they can be found such patients should not be sent to sanitaria for the cure of tuberculosis; a change of surroundings and life in the open air may accomplish more than any other method of treatment. The testimony of patients with chronic bronchitis, bronchiectasis, and emphysema, is practically unanimous that they are better during the warm months of the year. They undoubtedly do better leading an out-door life in a warm equable climate and in an atmosphere free from dust.

A tight thoracic binder will often relieve the pleuritic pain accompanying influenza pneumonia. The ice-bag is usually more efficient. If relief does not soon follow, or if the cough or dyspnœa are distressing, morphia should be used. With anomalous signs of pulmonary solidification exploratory puncture should not be delayed. The finding of elastic fibers in the sputum

may distinguish between abscess or gangrene and bronchiectasis. If the necrotic focus can be localized an operation should be performed. In one patient seen with C. L. Scudder complete recovery followed evacuation of a foul pulmonary abscess.

The physician should always have otitis media in mind in children with severe obscure symptoms. With predominance of nervous phenomena, meningitis should be suspected; if present, lumbar puncture will perhaps afford relief of symptoms—at least temporarily.

The convalescence should be carefully managed. A relapse may follow the too early resumption of customary duties. It may be weeks or months before complete health returns. Fresh air, nutritious food, and tonics may hasten recovery.

CHAPTER XVIII.

DENGUE.

By THOMAS D. COLEMAN, A.M., M D.

Synonyms.—Dandy fever, break-bone fever, stiff-necked or giraffe fever, scarlatina rheumatica, bouquet fever (corrupted into bucket fever), polka fever, knockel koorts, etc.

Definition.—Dengue fever is an acute infectious disease with two febrile paroxysms, sharp in onset, short in duration, characterized by intense headache, muscular and joint pains, irregular eruption, and terminating usually in recovery.

Historical.—The existence of dengue doubtless antedates any record that we have; but it was first observed in Spain during 1764–68. The first accurate descriptions were given by Brylon, of Java in 1779, and Rush of Philadelphia, in 1780. Accurate histories of epidemics of this disease have frequently been recorded. From its wide distribution it is not surprising to find it variously designated. The appellation dengue comes to us from the Spanish; by the Hindus it is called danga. These have been corrupted into dandy fever. Some have accounted for this term by the erect and stiff-necked appearance of certain ambulant cases. From the comparatively few patients who are able to avoid taking immediately to bed, dandy fever seems to the author more like an attempt at, and hence corruption of, dengue fever.

The other appellations of the disease are in attempt descriptive: *e.g.*, break-bone fever, from the intense muscular and joint pains; "giraffe," "stiff-necked," "polka," and "bouquet fever," from the attitude of body and the eruption; "scarlatina rheumatica," because of its eruption and joint manifestations; etc.

In 1780 an epidemic which assumed pandemic proportions occurred in India, Spain, and the United States. Rush first called attention to dengue in America in describing the epidemic in Philadelphia in 1780. It appeared in India in 1824. In 1827–28 it prevailed as an epidemic on the islands of St. Thomas and Santa Cruz to such an extent that but few of the entire population escaped. In 1828 an epidemic occurred in Charleston, in 1848–50 an extensive epidemic occurred not only here but throughout South Carolina, Georgia, Alabama, Louisiana, and Texas. In this epidemic, Wregg states that eight-tenths of the inhabitants of Charleston, and in Augusta, Ga., 8,000 out of 11,000 were affected.

From 1870–73 it spread over the whole of India. In 1871 it appeared in Arabia, extending south by lines of travel to Zanzibar and other towns on the East African coast; thence to Java and spreading over India. In 1873 it reached the Gulf States of the United States. This epidemic was general, and few escaped infection. In the city of New Orleans 40,000 persons contracted the disease. In 1880 an extensive outbreak appeared at Cairo, Egypt, attacking one-half the population, and rapidly spread throughout

Southern Europe. In the United States it occurred in North and South Carolina, Georgia, Florida, Mississippi, Louisiana, Texas, and Missouri.

In 1883 an epidemic occurred at Latakia, on the northern coast of Syria, but it did not spread at an elevation of 2,000 feet. In 1885 a severe epidemic broke out in Texas, appearing in Galveston, Houston, San Antonio, Austin, Dallas, and other smaller places. In 1895–96 it appeared at Bombay; and in 1895, 50,000 out of a population of 65,000 in Charleston, S. C., were attacked. In 1897–98 it appeared throughout Georgia, Florida, and Texas. In 1901 it was in Penang, and in Beirut, Syria, in which latter section few escaped infection. An epidemic of dengue also prevailed in the Isthmian Canal zone in 1904. Numerous minor outbreaks have occurred over widely distributed areas. According to Manson, it reaches pandemic proportions about every twenty years

Etiology.—Predisposing Causes.—1. *Climate.*—Among these the first and most important is climate. Residence in a tropical or subtropical country, and particularly on the coasts, water-ways and lines of travel, undoubtedly increases the liability to infection. The ordinary limit of diffusion is generally placed at from 32° 47′ N. to 23° 23′ S. While this is the rule, it has occurred outside of this zone; *e.g.*, in Philadelphia, New York, Boston, and other places. Outbreaks in these sections, occurring in the heated season, simply confirm the observation that warmth not only favors but is essential to its development.

2. *Season.*—It is strictly a disease of warm weather and disappears with the advent of winter; but in tropical climates it may occur during any month of the year. When it occurs outside of the regions mentioned it appears only during the heated season.

3. *Meteorological.*—Epidemics have occurred in both dry and moist conditions of the atmosphere; but, while a humid atmosphere is not essential, epidemics having occurred in both dry and wet seasons, it undoubtedly favors the spread of the disease. Altitude exercises an inhibiting influence.

4. *Race, sex, age, and social condition* do not exercise any influence. Filth, crowding, and unhygienic surroundings appear to favor its development.

5. *Individual Peculiarities.*—The physically deficient would, as in other infections, be the readiest victims; but, given a sufficient degree of virulence of infection, no individual is exempt.

Exciting Causes.—Until recently dengue was believed to be spread by the air, by contact with the diseased, and by fomities. While our present knowledge does not eliminate these, it is probable that Graham, of Beirut, Syria, has discovered the chief, if not the only, mode of infection. The history of the disease, its clinical features, and analogy, would lead us to believe it to be produced by a specific microörganism; and in 1885 McLaughlin, of Austin, Texas, found invariably a peculiar staphylococcus in the blood of patients, which he regarded as the causal organism. Graham has published a series of observations, which, if confirmed, will fix our knowledge of the etiology. He describes a hæmatozoan in the blood of dengue patients, which differs from that of malaria in its life-history, in that it never forms pigment. He thinks it resembles more closely the *Pirosoma bigemium* (*Boöphilus bovis*) than any other organism. He has never seen it in pairs nor received any suggestion that it multiplies by binary division. It possesses the power of amœboid movement, and is to be

found both in the body of the red blood corpuscle, from which it often projects motile pseudopodia, and also in the leukocytes, and floating free in the plasma. Furthermore it multiplies by sporulation. He found this same organism in the blood and stomachs of the *Culex fatigans* up to the fifth day after they had fed upon the blood of a patient with dengue; and he supports his belief that the disease is transmitted by the mosquito by the following experiments: He placed patients suffering with dengue in apartments which had been freed from mosquitoes and screened, and allowed healthy individuals to remain in close contact with those sick of the disease, and none so subjected developed dengue. He then took mosquitoes which were known to have bitten patients suffering with dengue, and carried them to a small village at a high altitude where dengue was unknown. Two healthy mountaineers allowed themselves to be bitten by the infected mosquitoes. Both developed dengue. The mosquitoes were all killed, and the subjects of the disease kept under mosquito bars until the symptoms of the disease had disappeared, with the result that no other cases developed. Graham also inoculated a human subject with a solution made from the glands of the infected mosquitoes; the patient had a chill on the third day and went through a typical attack of dengue.

Manson calls the motile parasite a plasmœba, and says it appeared to bore through the border of the corpuscle. The parasite was sometimes irregular, without pigment granules, gradually spreading and growing, often throwing out pseudopodia until it completely filled the corpuscle, the pseudopodia reaching beyond the border of the corpuscles and giving them a crenated appearance. It was actively motile. In a few hours spores would form in the body, the podia of the growth numbering six to ten. These would mature in a few hours, segment, burst out of the cell wall, and float freely in the plasma. The organism is much more active and smaller than the plasmodium malariæ.

Eberle, also, in 1904, found plasmæbic organisms in the blood of the *Culex fatigans*, and believes that this mosquito is the carrier of the disease. These researches would seem to make the chain of evidence complete, but Sutton, in 1905, states that in spite of the fact that repeated researches were made for microörganisms such as described by McLaughlin, "at no time was their presence demonstrated." He further adds that the non-pigmented piroplasma bodies like those seen by Graham, were frequently found in many of the unstained specimens. Inasmuch as they were also present in blood smears from a large number of cases of epidemic catarrh on board the U. S. S. Illinois at Newport News, some two years ago, it is probable that they are not foreign bodies, but simply the result of changes within the red cell. A stained specimen from the same subject invariably failed to show anything.

Pathological Anatomy.—In the epidemic at Galveston, Texas, in 1885 Paine observed a "localization of inflammation upon the serous membranes," especially the pleura and peritoneum. Hirsch mentions serous infiltrations in the vicinity of the joints, and reddening of the crucial ligaments of the knee joints. In addition, hæmatozoa have been described as occurring in the blood of dengue patients by such observers as McLaughlin, Graham, Manson, Eberle, Carpenter, and others.

Symptoms.—Dengue is a disease of three stages, *viz.*; (1) invasion lasting from two to five days; (2) remission, lasting from twelve hours to three days; and (3) a return of the symptoms of invasion, lasting from

twenty-four to thirty-six hours, in which none of the symptoms are as severe as during the first paroxysm. It has an incubation period of from two to five days, during which time no symptoms may appear, or the patient may experience a sensation of lassitude and anorexia. The onset is sudden. Some are attacked while at work; some awakened from sleep by the pains; and some while going up stairs, kneeling at prayers, etc. The onset varies with the severity of the attack, in some amounting to trivial discomfort and a few nervous symptoms; in others the invasion is sharp with severe physical and nervous manifestations. Prostration is intense, and is a prominent symptom. In children the disease may be ushered in by convulsions, followed by more or less delirium. Even in adults delirium occurs. In a typical case in adults there are few if any premonitions, the disease being ushered in by a feeling of chilliness, less frequently by a distinct chill. At the same time the patient experiences severe pains in the muscles and joints; these are sufficient to cause him to assume a more or less rigid attitude. The pains in the head, muscles, and joints, are severe, and in some instances excruciating, making one feel as if the very bones were broken. It is doubtless true, as noted by West, that the most lurid accounts of the suffering come from physicians who had the disease. The pains seem to affect every portion of the body, but are focalized in the head, back, legs and joints; they prevent rest, without an anodyne. The knee is the joint most frequently affected, but in some practically all are involved. The peculiar features of these joint manifestations are that while the pain may be intense, there is commonly an absence of swelling; and pain is not produced by pressure on the involved joint. Passive motion of the joint may be undergone without pain, but an effort of the patient to move it is attended by intense suffering. In other cases there is swelling of the involved joints, and pain is produced by pressure and even by passive motion.

There is a rise of temperature which is continuous until the end of the second, third, fourth, or fifth day, when it reaches its maximum. The temperature continues at this height until the third to fifth day, usually the fourth; is followed by a sweating and great prostration, when it suffers a remission, and in some cases an intermission, of twelve to thirty-six hours, after which there is a second elevation, which never reaches the former height. In some patients the second elevation of temperature and other symptoms are absent. The temperature varies from 100° to 106° F.; in cases of average severity not going above 103° or 104°; but in severe cases a maximum of 105°, or even 106°, is not infrequently found. The *pulse* is usually bounding, ranging from 90 to 140, and increases in frequency with the fever.

Anorexia is nearly always present, and in some cases marked nausea and vomiting. This last feature is prominent in some epidemics, and since dengue often occurs in close conjunction with yellow fever, has led to difficulty in diagnosis. This is more difficult when more or less jaundice and a heavily coated tongue are present. *The tongue* is usually moist, but covered with a whitish coat; in some cases it may be brown. The countenance wears an anxious look, and is congested from the attendant erythema, giving it a peculiar bloated appearance. The conjunctivæ are suffused.

The Eruptions.—There are two skin manifestations, the first a vasomotor erythema coming on with the first accession of fever, and the second, the true eruption, which occurs at the second accession of fever whether this follows

remission or intermission. The initial eruption varies in intensity from a simple redness to a distinct erythema. It occurs first on the face, causing it to swell; the conjunctivæ are suffused, and there is tumefaction of the eyelids. Sometimes this extends to the nasal and pharyngeal mucous membranes. It may also extend over the body. Its duration is short. The secondary rash, occurring usually on the fourth to the sixth day, is considered by many as one of the most characteristic symptoms. While this is true in a majority of cases, Bassett-Smith, West, and others, note its absence in many cases. Horlbeck states that in the epidemic in Charleston in 1895 the eruption occurred in 40 per cent. of all cases. Certainly the terminal eruption is present in a majority if not all cases. It appears first on the palms and backs of the hands, and extends up the arms; it is also found on the trunk, thighs, and legs. Generally it at first appears as a small elevated circular spot, dusky red in color, disappearing on pressure, and tending to coalesce with contiguous spots, making irregular patches some 2 or 3 inches in diameter. Between these areas the skin looks normal. In some instances, however, the entire integument may be covered by a continuous red blush, giving the patient a scarlatinaform appearance. It leaves in the order in which it appeared. It is characteristic in being not characteristic, some authorities describing it as urticaria-like, some as macular, some as measly, some as roseolar, rubeoloid, etc. These differences may be accounted for in large measure by the variations of the disease. The terminal eruption generally persists for twenty-four hours, but may last longer. When fully developed it is frequently accompanied by some itching and burning. It should not be forgotten that in some epidemics the terminal eruption is either absent altogether or is evanescent and escapes detection.

Desquamation follows the eruption, but is bran-like in character, and never appears in large flakes. It may continue for two or three weeks but is usually over in shorter time.

The bowels are at first constipated, but diarrhœa frequently supervenes toward the later stages. *The urine* is usually high colored, but is never suppressed and rarely albuminous. Enlargement of the lymphatic glands of the neck, axillæ, and groins not infrequently occur when the fever begins to remit.

Hemorrhages from mucous surfaces occur, but are by no means constant, being absent or of small consequence in a large proportion of the cases observed by me. They have been noted by various observers, however, and form a part of the symptomatology, Foster stating that "there is always a tendency to hemorrhages from the mucous surfaces, and, in females, especially from the womb." He states further that he had seen 3 cases of alarming hemorrhage from the bowels, 1 persisting for several months and finally causing death. He also saw 2 cases of black vomit, but these are extreme cases.

Immunity.—Our present knowledge does not justify the position that any race or generation of people is immune. Recorded epidemics show that the people of a city are attacked rapidly, in large numbers, and without regard to race, sex, age or caste. One attack usually protects against another, but two and even three attacks have been observed in the same individual. Dickinson records in the epidemic in Charleston in 1850, that only those escaped the disease who had suffered from it in 1828. A few writers on

dengue hold that one attack affords no protection against a second. In this the writer does not concur.

Complications and Sequelæ.—Among these may be mentioned; (1) hemorrhages from mucous surfaces; (2) inflammations of serous membranes; (3) delayed convalescence; (4) relapses. Hemorrhages from mucous surfaces, while in some epidemics sufficient to constitute a symptom, are absent in the majority and may be regarded as a complication. These occur from the nose, stomach, intestines, and uterus. In rare instances, pleurisy, orchitis, pericarditis, endocarditis, and meningitis, have occurred. Abortion or miscarriage may occur. Convalescence is often slow, extending over weeks and months, and soreness of the muscles and joints may persist or recur at intervals for a long time. Relapses occur a second and even a third time, but usually one attack protects against another.

Diagnosis.—The only diseases with which it is apt to be confounded are yellow fever, influenza, malarial fever, acute articular rheumatism, and scarlatina.

Yellow fever is a disease of one febrile paroxysm, dengue of two. Yellow fever is a disease of shorter duration. In dengue the pulse is *accelerated* in proportion to the temperature. In yellow fever the pulse is not quickened with the temperature, but slowed. In yellow fever, an eruption is usually not present, whereas an initial and terminal eruption are frequently present in dengue. Black vomit and jaundice occur with yellow fever while they are generally absent in dengue. The muscular and joint pains of dengue are not present in yellow fever. The mortality of yellow fever is 30 per cent., while it is almost *nil* in dengue. In like manner while the diseases do occur coincidently, the nature of the epidemic is of value. Lastly, the examination of the blood should distinguish if the hæmatozoan dengue be confirmed as the causative agent.

Influenza most frequently prevails during a cold season when dengue could not develop. Influenza is a disease of one febrile paroxysm, and is accompanied by acute catarrhal symptoms in strong contrast to dengue. Finally, the nature of the epidemic and the presence of the influenza bacillus should make the diagnosis comparatively easy.

Malarial fever, while occurring most frequently in the same sections, and at the same seasons of the year, does not occur in such epidemic form. The febrile disturbance differs from that of dengue, and is relieved by quinine, whereas this drug has no effect on dengue. Finally, the presence of the plasmodium malariæ in the blood would make the diagnosis positive. Dengue should not be confounded with articular rheumatism, for the reason that this latter disease does not occur in epidemics. The febrile paroxysm is different, being irregular and longer in rheumatism. Again, the mortality and complications of the latter disease are far more serious. Pressure on inflamed joints in rheumatism causes acute pain, whereas in dengue it usually does not. It would seem to resemble scarlatina only in the rash and fever; but since scarlatina is largely a disease of childhood while dengue attacks all ages, and scarlatina occurs in all seasons while dengue occurs only in warm weather, and scarlatina is accompanied by the characteristic "strawberry tongue" and ulcerated fauces, is a disease of one febrile paroxysm, is not attended by muscular and joint pains, and is followed by extensive desquamation, the diagnosis should at no time be in doubt.

Prognosis.—Except in those already affected with other disorders the mortality is almost *nil*.

Treatment.—**Prophylaxis.**—So long as a susceptible individual is in the epidemic area, absolute protection is almost impossible. If the *Culex fatigans* is responsible for the transmission much would be gained by warfare against this insect. Whether infection is conveyed by the mosquito, by contact with patients, or fomities, those having the disease should be isolated. The debilitated should receive wholesome food and tonics.

Diet.—The diet should be liquid; when marked anorexia is present, often the only nourishment that will be retained is egg albumin. The diet should receive especial attention not only throughout the attack, but in convalescence, for no such benign disease with the possible exception of influenza, which is more fatal, produces such marked prostration and has frequently such a tardy convalescence.

External Applications.—Hot baths reduce the temperature and quiet the nervous system. When these fail to reduce the temperature, or cannot be given from the pain attendant on movement, cold applications may be made to the head, and the body sponged. The pains being so widespread, local applications have a limited value; but much comfort may be given by rubbing the back and joints with a liniment of equal parts of oil of wintergreen and spirits of camphor.

Medical Treatment.—The bowels should be well moved, preferably with broken doses of calomel. An adult should be given gr. $\frac{1}{4}$ (0.015 gm.) every half hour until two or three grains have been taken, and in children in proportion to the age. If the bowels fail to move in eight hours a saline aperient should be given. The three more urgent symptoms are pain, fever, and insomnia. In cases of moderate severity a pill consisting of salicin gr. v (0.33 gm.), and Dover's powder, gr. j to ij (0.13 gm.), will suffice, being repeated every four to six hours as indications warrant. The coal-tar derivatives are especially valuable and phenacetine or antipyrine with codeine and citrate of caffeine may be given. The following pill three or four times a day, if necessary, will be found efficacious in a majority of cases: phenacetine—gr. v (0.33 gm.), codeine—gr. $\frac{1}{4}$ to $\frac{1}{2}$ (0.015 gm.), caffeine citrate—gr. 1 (0.065 gm.).

When the joint symptoms are severe the salicylates, alone or in combination with an opiate, will be found effective. In a certain number these will not avail, and morphine will be indicated either by mouth or rectum, but a hypodermic of gr. $\frac{1}{4}$ (0.015 gm.) will be found most efficient. This must be repeated as necessary. It practically always gives relief. Quinine may be given for its antipyretic effect, and it may perhaps have some influence on the hæmotozoan; but so far as known it has no value as a prophylactic and does not cut short the disease. Some authorities consider it not only valueless but harmful. There is no treatment known which aborts an attack, and the treatment consists largely in regulation of the diet, keeping the patient as comfortable as possible, and meeting symptoms as they arise.

CHAPTER XIX.

EPIDEMIC CEREBROSPINAL MENINGITIS.

By HENRY KOPLIK, M.D.

Definition.—Cerebrospinal meningitis, or cerebrospinal fever, is an acute infectious disease with a characteristic local lesion in the meninges and tissue of the brain and spinal cord.

There have been various synonyms for the disease according as each author in past epidemics has considered certain symptoms a prominent feature of the affection. Thus the disease has been called "spotted fever" from the fact that at the outset and in the course petechiæ and other eruptions occur on the surface of the body. In some epidemics the petechial eruptions have been so marked and so extensive as to give rise to the name, "black death." Such was the case in an epidemic occurring in Ireland.

Cerebrospinal fever is a term which has been preferred by Osler in an attempt to compare the affection with pneumonic fever or pneumonia. It is certain that he has shown a striking similarity in the course of both affections. The term cerebrospinal fever, however, expresses one part of the symptom complex and does not include the lesions found in the brain and cord. We will, therefore, adhere to the term cerebrospinal meningitis of the epidemic type, because the striking feature of the disease is that it appears, when prevalent to any extent, in the form of epidemics and is primarily a meningitis of the brain and cord, which seems to be the prominent feature of the disease and which has attracted the attention of authors and investigators of all times.

History.—Cerebrospinal meningitis may be termed a disease of the American continent, and it is not improbable that the contention of the European authors that the disease has spread from America to Europe has much support in fact. The disease first appeared in modern history in 1805, in Geneva, in midwinter and spring of the year, and was described by Vieusseaux. Coincident with this it appeared in Medford, Mass., and was there described by Danielson and Mann independently of Vieusseaux. From Medford, Mass., the disease spread throughout New England and was prevalent to a greater or less extent until 1816. Among the historians of the disease at this time was Elisha North and a committee of the Massachusetts Medical Society made up of James Jackson, J. C. Warren and Thomas Welch. An epidemic in Litchfield in 1807 was described by Woodward; and in 1808, Bestor, Fiske and Williamson of Baltimore described outbreaks. Hirsch divides the occurrence of the disease, first, into a period in which it was prevalent in epidemics in various parts of the United States particularly, and in Europe. This extended from 1805 to 1830. In this period the disease was seen in Canada, in Virginia, Kentucky, Ohio, New York and Pennsylvania, up to the year 1828, and from this up to 1842 the United States was free of epidemics. In the second period the disease seems to have been more prevalent in France and Denmark, especially among troops. In the third

period Sweden and Germany seem to have been most affected. This period extends over ten years and includes the descriptions of Wunderlich, von Ziemssen, Hirsch and Klebs. The latter described an epidemic in Berlin and included an intimation as to its essential cause, so beautifully worked out by Weichselbaum. From 1850 to 1875 there were epidemics in the United States and in Ireland; the latter in 1866, occurred in Dublin and was particularly fatal, being called the "black death." The fourth period extended from 1881 to the present time, although Hirsch does not include any epidemics subsequent to 1890. This last period must include the work of Leyden, von Ziemssen, Bauer and Leichtenstern, who have described sporadic cases and small epidemics in the Rhine provinces. In 1893 the disease appeared in New York and Lonaconing, Md. In 1896 there was an epidemic in Boston, and in 1904 and 1905 one of the most widespread epidemics in the history of the disease appeared in New York.

From this it would appear that America is peculiarly the home of this disease, and it is very difficult in studying the literature and epidemiology to account for this fact.

Character of the Epidemics.—Councilman has attempted to characterize the nature of the epidemics of this disease as distinct from epidemics of other diseases, such as cholera. Certain it is that the disease first appears in isolated places and does not seem to be carried to any extent from one place to another, though it has been shown in Algiers and in France that the disease may be traced along the line of march of troops. No such etiological factor, however, can be pointed to in the epidemics in Boston and New York.

In the author's experience and in that of most writers the disease is most prevalent in the winter and spring. The epidemic of 1904 first appeared in New York with isolated cases in February. The frequency increased and in April and May the largest number of cases occurred. In summer and autumn the disease died out, to reappear late in the winter of 1905. In Boston the first case was observed in June and the disease became epidemic only in February, the greatest number of cases being in March, April and May.

It is a disease of young people, but the prevalence in the Boston and New York epidemics seems to have varied as far as the age was concerned. Children were most affected in the New York epidemic, whereas in Boston the greatest prevalence occurred from the twenty-sixth to the thirtieth year. Leichtenstern shows that in his material the greatest number occurred before twenty years of age, but the greatest frequency between the ages of fifteen and twenty years.

Contagion.—The question of the communicability of the disease has always been a matter of discussion. There can be no doubt that in certain epidemics, such as that described by Berg in 1893 in New York, there was no instance of the affection of more than one person in a family, whereas in 1904 and 1905 numerous examples have occurred in which two, three, and even four children of a family were affected. The author, in some of these cases, found that another child of the family, having slept in the bed recently vacated by the meningitis patient, contracted the disease. It may be carried from one person to another or from one country to another, according to North, but there has been no authentic example of this in recent times to the knowledge of the author. That is, cerebrospinal meningitis cannot be carried as scarlet fever may, by a second person to a third. It occurs in certain houses, very much in the manner of pneumonia.

One attack does not protect from another; this has been shown by North, Herman and Kober, who recorded instances of second attacks, some within a year.

There is no doubt that the disease is more prevalent in the crowded quarters of cities than in the sparsely populated parts and where filthy conditions exist than in more cleanly portions. This has been doubted by some, because cases have been found in the better quarter of cities where the hygienic conditions were good, but the author feels that a careful study of such cases will reveal that they are exceptional and have been communicated or conveyed from a filthy and crowded quarter of the city where the disease is most prevalent. Such cases occurred in the recent epidemic in New York. Children from the poor and filthy quarters of the city who could afford to do so were attending better-class schools in the more hygienic part of the city; they contracted the disease, and some of the cases occurring in the better part of the city could be traced, possibly, to contact with some one from the poor quarter.

The disease occurs in sporadic as well as epidemic form. Both are due to the same cause. The sporadic cases occur either independently of the epidemic, that is, in different quarters of the city, or in sparse numbers so as not to amount to epidemics. Such has been the case in the author's experience in the five years prior to 1904, when sporadic cases occurred throughout the City of New York. Sporadic cases may occur for some years after an epidemic has run its course. It is not understood why epidemics are not prevalent at such periods. Some have tried to explain these sporadic cases by the morphology of the *Diplococcus intracellularis*, its low vitality and the immunity of the mass of individuals to infection by it, and by the absence of conditions favorable to epidemics and the communication of the disease by one individual to others.

That the disease is communicable from person to person there is no doubt, although this varies in different epidemics, being scarcely apparent in some. It certainly is not communicated through the atmosphere, as scarlet fever or measles.

The general conclusion is that it may be communicated through the secretions of the mouth, nose and conjunctiva, because the etiological factor of the disease has its habitat on the mucous membrane of these localities and has been demonstrated, as in one of the author's cases, in the secretion of the conjunctiva and nasal mucous membrane. It has not yet been determined whether the disease is communicated to human beings by insects.

Etiology.—The etiological factor both in the epidemic and sporadic forms, is a coccus of the diplococcus type. It was first described by Leichtenstern in five cases of the disease, and more completly isolated and described by Weichselbaum in 1887. It is a diplococcus similar to the gonococcus and has been called by Weichselbaum the *Diplococcus intracellularis meningitidis*. This diplococcus is the essential cause of the disease and has been found in all authentic cases of epidemic cerebrospinal meningitis. It has been described by Goldsmith, Netter, Jäger, Heubner, Peterson, Fürbringer and Finkelstein. An attempt to nullify the unity of the affection by tracing some cases to the pneumococcus has been abandoned and it is no longer recognized as an etiological factor in the epidemic form of this disease.

The *Diplococcus intracellularis* is a micrococcus of the size of the ordinary pathogenic micrococci. The diplococci have an unstained interspace, are

decolorized by Gram's stain, may occur in tetrads or in short chains, but do not occur in the form of streptococcus chains, as described by Jäger. The microörganism is difficult to cultivate and of low vitality. Cultures, in order to be kept alive, must be renewed at short intervals. It grows best on Loeffler's serum and in glycerine-agar, not in the form of profuse streaks but rather in isolated colonies. It grows but feebly in plain agar and is not visible as a growth on potato. In bouillon it gives a slight cloudy sediment at the bottom of the tube. It does not change litmus.

In the inflammatory exudate it is especially prevalent in the polynuclear leukocytes, not in the other cells of the tissues, though it may occur outside of polynuclear leukocytes, either in the exudate or in the tissues but not in the cell body. It sometimes is so numerous as to pack the leukocyte and in other leukocytes may not be so numerous. It has been found in certain cases in great numbers in the lungs when pneumonia complicated the meningitis, and here it may occur with pneumococci, staphylococci and streptococci. It is not pathogenic to guinea-pigs and rabbits in subcutaneous injections, but will kill the experimental animal after intrapleural, peritoneal or subdural injections. It is pathogenic to goats in peritoneal, subdural and intrapleural injections, but this seems to be the only animal, excepting the monkey, in which the picture of the disease, as it appears in the brain and cord, has been reproduced.

The meningococcus has been found in the secretions of the nose, the eye, the bronchi in pneumonia, in the pus of complicating joint affections and in the blood, as well as in other localities hitherto mentioned. The meningococcus has been isolated from the blood of patients suffering from epidemic cerebrospinal meningitis by Solomon, Moller, Bettencourt, Franc and Elser. The last-named writer found it in 25 per cent. of his cases at various periods of the disease independently of the severity of the infection. Its occurrence in the nose and the secretions of the nasal mucous membrane of normal individuals is especially interesting in view of the fact that in this locality there occurs normally a diplococcus which closely resembles the meningococcus and which is called the *Diplococcus catarrhalis*. This micrococcus has been mistaken by many observers for the meningococcus. Its morphology has been carefully worked out by Ghon and Albrecht, and by the skilled observer can be easily distinguished from the *Diplococcus intracellularis*. The *Diplococcus intracellularis* has been found in the nasal secretion by Schiff and Burdach not only in those who have been in contact with cases of meningitis but in the secretions of the nasal mucous membrane in the normal individual. Wright has recently described a case in which he has isolated the meningococcus from the nasal secretion of a case which closely resembled one of ordinary influenza.

Goodwin and Scholly isolated the meningococcus from the nasal mucus of 50 per cent. of meningitis patients during the first two weeks of the disease and from 10 per cent. of those who came in contact with the patients. These authors, as well as Boldnan, consider the disease transmissible through the nasal mucus from one person to another.

Considering all the data, weight is given to the supposition that the mucous membrane of the nose and the neighboring respiratory spaces is a normal habitat of the meningococcus. This diplococcus is found in the pus of the conjunctivitis which complicates the disease and at least one such case has been published by the author.

The question of the method by which the infectious agent gains access to the cranial cavity is a matter of great speculation. The old theory of Weigert that the infection occurs through the mucous membrane of the nose and ethmoid sinuses has been revived in another form by Westenhofer. The latter contends that the disease is an inhalation infection by way of the lymphatics through the tonsils, sphenoidal sinuses, the antrum of Highmore and, finally, by direct extension through the sphenoidal sinuses to the hypophysis. In this manner all cases of cerebrospinal meningitis would be basic at the start. He rejects entirely an extension of the infection to the brain through the ethmoid sinuses inasmuch as they are rarely inflamed. Unfortunately a critical inspection of Westenhofer's work is not convincing.

Morbid Anatomy.—The essential lesions are inflammatory changes in the meninges of the brain and cord, the tissue of the brain, cord and nerves.

The Brain.—The *meninges of the brain* are inflamed and there is a purulent, seropurulent or fibrinopurulent exudation, most apparent at the edges of the brain, extending from the optic commissure back over the crura, pons and medulla. On the surface the exudation is found on the convexity, mostly laterally and for some distance on either side of the fissure of Rolando. Little or no exudate is found along the longitudinal fissure. The meninges of the cerebellum are also involved, principally on the upper surface and upper rim along the choroid plexus. There is some exudation in the sulci.

In acute stages the changes consist mostly of injection and œdema of the meninges. There is little or no exudate. There may be thin lines of yellowish exudate along the sulci and the pia-arachnoid has a pinkish color due to the intense injection of the bloodvessels. (Plate XIX.) In cases dying five to twelve days after the onset the exudate is more abundant and fibrinous and more marked about the base and medulla. In cases which have lasted from fifteen to thirty days there is œdema and thickening of the meninges, with whitish patches apparent on the vertex and at the base, consisting mostly of organized exudate. At the base of the brain bands of organized tissue may be seen stretching from point to point. The lining membrane of the ventricles may be thickened and the seat of exudate.

The *meninges of the cord* are affected very much in the same manner but to a less degree. In some cases there is little or no exudate; even in cases which have lasted a week and which show marked exudate on the brain there may be little or none visible macroscopically on the cord. Exudate on the cord is most marked on the posterior surface, the amount of subarachnoid fluid being increased and the central canal dilated. (Plate XX.) In acute cases the ventricles of the brain may not only be dilated but filled with turbid fluid, and the cornua may contain a purulent fluid. The lining membrane, or ependyma, is the seat of changes either of injection or exudate, as is also the choroid plexus. The tissue beneath the walls of the ventricles may be œdematous and softened. In chronic cases the lining membrane is thickened and has lost its lustre. It may be covered with granulations. The cavity of the ventricle is dilated to a varying degree, according to the amount of hydrocephalus which supervenes.

The *tissue of the brain* may be the seat of hyperæmia, or hemorrhages in the various parts, and on section there may be thrombi in the vessels, with areas of softening and even abscesses in places. The cranial nerves are found to be embedded in the exudate and on section are swollen and red and the seat of changes to be described. On microscopic examination the tissue

PLATE XIX

FIG. 1

Convexity of the Brain. Epidemic cerebrospinal meningitis with death on the fifth day of the disease. Purulent exudate.

FIG. 2

Lateral View of the Brain in the Same Case.

PLATE XX

Section of the Spinal Cord, showing the Exudate on the Surface, More Marked Posteriorly and Involving the Anterior and Posterior Nerve Roots. Epidemic cerebrospinal meningitis in an adult; death on the fifth day of the disease.

of the pia-arachnoid is found to be the seat of purulent infiltration, the bloodvessels are filled with blood and leukocytes and their walls show infiltration with small masses of leukocytes. Throughout the tissue of the pia-arachnoid there are found small areas of leukocytes scattered in the finer granular inflammatory mass. The connective tissue of the pia is infiltrated with cells, principally polynuclear leukocytes. (Plate XXI.) There is a peculiar cell found here, and described by Councilman, which measures two to eight times the diameter of the leukocyte, having a large vesicular nucleus and finely granular protoplasm in the cell body. Some of these large cells contain a varying number of leukocytes.

In chronic cases the pia-arachnoid shows distinct changes in the connective tissue resembling cicatricial tissue. There is proliferation of fixed connective tissue cells of the arachnoid and those lining the lymph spaces. Nuclear figures are very common in the cells of the connective tissue. Changes in the meninges of the cord resemble in a general way those found in the pia-arachnoid and brain.

The brain tissue shows microscopic changes, which are most marked in cases which have extended over a period of five to ten days or more. The vessels are injected, the tissue itself is œdematous, and the lymph spaces are dilated. Here and there there is a diapedesis of leukocytes from the meninges into the brain tissue proper some distance from the cortex. There are areas of hemorrhage and extensive softening at times. The ganglion cells show changes of a degenerative nature, although investigations on this point are not yet complete. In chronic cases also the canal of Magendie may be obliterated and there may be marked changes, thickening of the meninges, with connective tissue proliferation into the tissue of the brain. The neuroglia shows in places an increase of cells, especially with vesicular nuclei and branching processes in the cortex of the brain and in the walls of the ventricle. In the cord itself these changes in the neuroglia are not so common, and the changes in the ganglion cells, so far as is known, consist of granulation, atrophy, and fatty degeneration.

The microörganisms which are the essential cause of the disease are found in the exudate on the surface and in the tissue of the pia-arachnoid, for the most part in the leukocytes. Very few are found outside these cells. The *Diplococcus intracellularis* may also invade the tissue proper of the brain and spinal cord, although in the majority of cases this is not as marked as one would expect from the extent of the inflammatory lesion found on the surface.

The Nerves and Ganglia.—The changes in the nerves have been particularly studied in the optic, the olfactory, the fifth, seventh and eighth nerves. Changes in the ganglia have been studied in the Gasserian ganglia, and are well described by Councilman.

The changes in the nerves consist of infiltration of the pia-arachnoid and dilatation of the bloodvessels of the nerve with a purulent infiltration as a direct extension from the inflammation of the brain. In the optic nerve the extension of the inflammation may reach the optic globe, causing neuroretinitis, and may even proceed to a general inflammation of the tissues of the orbit with bacterial invasion. In chronic cases the nerve may be the seat of chronic changes. In other words, the cranial nerves are the seat of a more or less extended neuritis which varies from an exceedingly mild infection to that of the severest type.

The ganglia, such as the Gasserian ganglion, may be the seat of purulent infiltration and degeneration to such an extent as to result in the destruction of the cells. The posterior nerve roots of the spinal cord may be the seat of inflammation, the bloodvessels are injected, small collections of plasma and lymphoid cells are found between the individual nerve fibers, which are themselves the seat of degeneration, and the axis cylinder may show marked changes. The peri- and endoneurium are the seat of infiltration and inflammation. In some cases the pituitary body has been found to be the seat of infiltration, necrosis, and atrophy of the gland elements.

Other Organs.—The changes found in other organs of the body are either complicating or accidental. A complicating pneumonia may be of the lobular or croupous type. There may be bronchiectasis and small hemorrhages throughout the lung. In some cases the pneumonia may be due to the pneumococcus. In other cases, such as recorded by Councilman, the pneumonia was directly caused by the *Diplococcus intracellularis meningitidis*, and the microörganism was found in great numbers in the inflammatory area.

The spleen in some epidemics has been found to be enlarged in the majority of cases. It may, however, be smaller or even normal in size. After the fifth day, as a rule, it may be slightly enlarged and the seat of hyperæmia. The lymphatics show no changes outside of congestion and injection. The liver may show cloudy swelling, and in exceptional cases purulent infiltration, especially in the portal spaces. The kidney may be the seat of acute degeneration and parenchymatous changes.

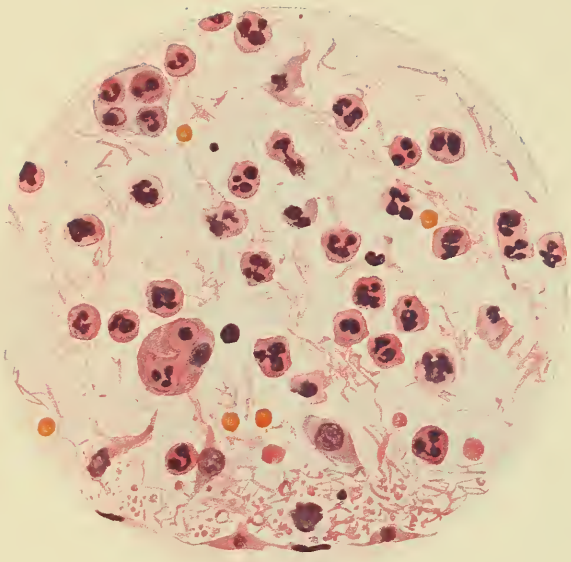
The changes in the skin correspond to the lesions found in this disease. There are areas of hyperæmia and hemorrhages, most marked in the subcutaneous fat. These correspond to the petechiæ in the skin seen during life. Although there may be abscess in the skin and purulent infiltration, as yet the intracellular diplococcus has not been found in the skin lesions. In the herpes, both on the face and the trunk, no diplococci have been isolated from the fluid, but there is purulent infiltration and increase of the fixed cells of the tissues.

Classification.—Under the heading of cerebrospinal meningitis or cerebrospinal fever there have been hitherto included certain forms of meningitis which have occurred in groups more or less extensive and which are now not recognized as the form of cerebrospinal meningitis of which we are at present writing. At one time such authors as Netter, in France, thought that the pneumococcus form of meningitis might occur in epidemic form. However this may be, we recognize to-day that cerebrospinal meningitis, or cerebrospinal fever of the epidemic type, is due to a single etiological factor—the *Diplococcus intracellularis* of Weichselbaum. The meningitis of the epidemic type is caused primarily by this microörganism, and investigators are agreed that in all epidemics this one organism has been the etiological factor. Small outbreaks and sporadic cases of the same disease occurring in years in which epidemics were not prevalent have been proved to be due to the same microörganism. The old question as to the essential cause of the sporadic cases of cerebrospinal meningitis of the epidemic type can be regarded as settled.

Symptoms.—Cerebrospinal meningitis of the sporadic or epidemic type manifests itself in distinct clinical forms. During an epidemic these are more sharply defined than at other times.

The first is the so-called foudroyant or malignant form in which within twelve, twenty-four, or thirty-six hours the fatal issue may supervene. In an

PLATE XXI



The Exudate of the Early Stage and Inflammatory Reaction in the Pia Mater.

This shows: Swelling cells of the pia; fibrin in the exudate; the leukocytic invasion; new connective-tissue cells; nuclear division; large cells containing three or more leukocytes described by Councilman, Mallory, and Wright. Eosin and hematoxylin stain.

epidemic these malignant forms are not uncommon. They are most apt to appear, however, either at the outset or at times when the epidemic is apparently on the wane. An adult or a child in apparent health complains of slight headache, there is nausea followed by vomiting, fever and unconsciousness in rapid succession. Death occurs in a short time, consciousness not being regained.

Another form is that in which the patient, in apparent health, is suddenly taken with dizziness or vertigo, vomiting occurs, followed by severe headache, generally of the occipital type; fever ensues, the patient becomes drowsy or even delirious. At this time there may be slight rigidity of the muscles of the neck and a slight Kernig reaction. In these cases, after a period varying from a few hours to a few days, the patient passes into a condition of stupor and delirium, with retraction of the head, opisthotonos, the Kernig symptom and the full picture of the disease. In other cases this history is interrupted by periods of collapse. A patient taken with fever, vomiting, and headache, is ill for twelve hours with these symptoms and is perfectly conscious, when suddenly, after an attack of vomiting, he goes into a condition of collapse, with a rapid thready pulse, sighing respiration and total abolition of reflexes. After rallying from this condition the patient shows the classical symptoms of cerebrospinal fever. In this condition of shock there is nothing characteristic of meningitis; that is, there is no rigidity of the neck, opisthotonos, or Kernig's sign. The patient seems to be in the condition of shock superinduced by the sudden onset of the disease and the toxæmia resulting therefrom, and what has appeared to the author rapid distension of the ventricles of the brain with fluid exudate.

During an epidemic there is a more puzzling form very frequently encountered. A patient previously in apparent health will complain of headache, has fever, and, in the case of infants, is restless, refuses the breast, vomits once or twice, and then has a temperature curve ranging from 105° F. to normal or subnormal. In the intervals of apyrexia the patient seems quite well and, in the case of infants or children, will play and seem in apparent health. When the temperature rises, however, they complain of slight headache, become drowsy and irritable, and refuse nourishment. In these cases the typical signs of meningitis are not always apparent. The delirium is not constant and may not extend over twenty-four hours. The rigidity at the back of the neck may not be very marked, especially in the case of young infants. If above two years of age Kernig's sign may be present, not only when the temperature is high but when subnormal. The most characteristic symptoms, however, seem to be the sudden onset, and the prolonged period of fever, which is of the intermittent type. These cases are often mistaken for malaria and are not uncommon in an epidemic of cerebrospinal meningitis.

In many of these cases the onset has been insidious; in others it may have been marked by an attack of vomiting or convulsions. In other cases the disease is rather masked by some complication such as neuritis. The writer has seen certain cases in which the onset has been marked by slight headache, vomiting, and fever, which continued for a few days, and then the patient developed an intermittent temperature in the absence of headache, with but slight rigidity of the neck and with a marked Kernig's sign and severe double sciatic neuritis, which continued over weeks with intervals of intense pain and the characteristic temperature, and resulted in final recovery.

In every epidemic of cerebrospinal fever there are abortive cases which last but a few days when the fever subsides and the patient makes an uncomplicated, at times a complicated, recovery. The abortive cases, epidemic or sporadic, which the author has met, begin in the classical way. Patients complain of headache, may vomit or have a convulsion, with high temperature; there is severe headache for a few days, with rigidity, and the symptoms which will be described as characteristic of the disease, ending finally in complete recovery, or leaving the patient totally deaf. These are not so uncommon as would be supposed, and are not generally recognized because their duration is so short.

Finally, the regular type is that met with in the sporadic and epidemic cases. A patient in apparent health is taken with sudden severe headache, vomiting, fever, and a rapid pulse. The vomiting may not persist beyond the initial stage, but the headache continues and increases, rigidity of the neck becomes apparent, and after a few days, opisthotonos may set in; stupor and coma develop, and the patient goes on to the symptoms of the acute or subacute forms.

Under the acute classical form we may include those cases which last from one to four weeks and either die or recover with or without complications. Under the chronic form we understand those cases which last from two to three or four months and either make a recovery with sequelæ or complications, or die of exhaustion.

The Mode of Onset.—In the vast majority of sporadic and epidemic cases the main characteristic of the onset is that it is sudden and abrupt. Patients have previously been in apparent excellent health when they are stricken with the disease. There is a history of gradual onset in a very small percentage, and the writer believes that in these there may have been a previous indisposition to alter the history of the onset. In this respect this form of meningitis differs from the secondary forms, especially the tuberculous, in which the onset is usually gradual.

When fully developed the clinical features presented by a case of cerebrospinal meningitis of the epidemic type are quite characteristic. The patient lies in a semi-conscious, stuporous, delirious or comatose condition. The position most affected by the patient in bed is that on the side in the crouching posture, the head retracted, the knees drawn up, the arms flexed, the hands supporting the chin. In some cases there may be an eruption on the body, either petechial, roseolar, or erythematous. There is generally high temperature which may at times fall to normal or subnormal. The patient may toss here and there in bed or may lie, when undisturbed, in a muttering delirium or, when disturbed, may show signs of hyperæsthesia of the nervous system.

Another clinical type which occurs both sporadically and in epidemics is that which affects children below two years of age. It is the so-called posterior basic type of meningitis, which has been described by Gee and Still under the title, at first, of cervical opisthotonos and later, by Still, under the title here given. In these cases the meningitis confines itself almost exclusively to the structures at the base of the brain, from the optic chiasm backward to the pons and cerebellum. These cases are for the most part fatal, developing hydrocephalus in course of time, and in exceptional cases resulting in recovery. This form will be treated at greater length by itself.

The so-called tâche cérébrale is present. When an attempt is made to straighten the neck there are evidences of extreme pain. If the pupils are

closely watched during this, distinct mydriasis can be seen. In children close observation of the eye reveals an automatic oscillation to and fro on the horizontal axis. The pupils may be contracted or dilated, according to the stage of the disease. When the patients are suffering pain the pupils are seen to dilate. An attempt to extend the leg on the thigh when the latter is at right angles to the trunk not only meets with resistance but is also accompanied by evidences of pain. This will be described under the so-called Kernig symptom. The pulse in the acute cases is rapid, at times irregular, but latterly as slow as in tuberculous meningitis. The respirations may be sighing, shallow, sometimes imperceptible but rarely of the Cheyne-Stokes variety, as seen in tuberculous meningitis.

The patient may not only resist any interference but all nourishment. In some cases there are intervals of consciousness during which they complain of intense headache, usually of the occipital, sometimes of the frontal type, and sometimes of pain along the spine. Some patients complain of abdominal pain. After continuing in this condition for a varying length of time, the patients may regain consciousness and gradually improve but the last thing to disappear before convalescence is the rigidity of the neck and the contractures of the limbs. As convalescence approaches there may be intervals during which the patient complains of headache and the temperature rises, and intervals in which he is quite comfortable; or he may regain consciousness or pass into deep coma, from which he never rouses, having progressive retraction of the head, opisthotonos, emaciation and coma.

In other cases patients may pass into a chronic stage during which some of the symptoms, such as stupor and delirium, may abate. The fever continues, however, over a period of weeks, with intervals of headache and pains in the limbs, especially along the sciatic nerves. In some of these cases emaciation is one of the most marked symptoms. Recovery from this condition may occur gradually.

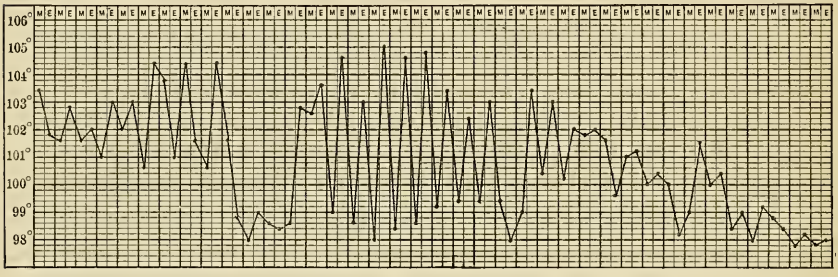
Individual Symptoms.—We may divide the symptoms into those which are especially referable to the effect of the toxins and the bacterial invasion, such as fever, etc., and those connected more particularly with the reaction of the general nervous system.

Fever.—The temperature is not characteristic. In some cases the temperature is of a decidedly irregular type, more especially in those patients in whom the duration of the disease is short. Cases of a week's duration will show a gradual rise from the onset to a certain point and then a gradual decline. In this respect the temperature curve is no more characteristic than that seen in typhoid fever of short duration. In other cases the fever curve is exceedingly irregular and may extend over a week, with remissions and intermissions; that is, the temperature may drop a degree or two, or at times to normal or subnormal, and mount again to its original height or a degree or two lower.

In another class of cases the fever seems to take a distinctly intermittent course and these, it seems, are the cases which have been mistaken either for malarial fever or typhoid in the later stage. In these cases the temperature makes exceedingly wide excursions and may mount on the same day to 105° or 106° F. and drop within a few hours to normal or subnormal, to return within a few hours to its original height. Such a temperature may continue for weeks, and in this respect, if combined with other symptoms of cerebrospinal meningitis, must be regarded as characteristic of this set of cases.

In the subacute or chronic forms, especially those occurring in children below two years of age, the temperature after a time may drop to normal and continue normal for weeks or at most half a degree or a degree above it, in this respect simulating very closely what is seen in tuberculous meningitis. In older children and in adults the temperature in the subacute period may also drop to the normal and after some days mount again. The temperature does not seem to be dependent on bacterial reinvasion or exacerbation of the symptoms in these subacute and chronic cases. The patient appears to be in much the same condition, with the exception of the temperature falling to normal and remaining there for days, mounting again in irregular fashion.

Fig. 61.



Temperature curve showing irregularity and wide excursions.

During convalescence a patient who has been doing fairly well may suddenly develop an intermittent form of fever. In these cases at times we have with this temperature a slight return of the former symptoms, such as headache and at times vomiting. These seem to be more in the nature of a relapse. In some of these, apparent convalescence may be interrupted by a week or two of recurrent fever which finally disappears, with complete recovery of the patient.

Pulse.—The pulse is, as a rule, rapid. It may range from 90 to 120 in the course of twenty-four hours and is irregular both in rhythm and force. This irregularity may be said to be quite characteristic of these cases. As to rate it differs from the tuberculous form, in which the pulse is characteristically slow.

Respiration.—The respirations may be irregular, sighing, superficial or deep. As a rule the rate is increased in frequency to a varying extent. The Cheyne-Stokes respiration is not as common as in the tuberculous type, but the irregular sighing form of respiration is very common.

Skin.—The eruptions vary according to the nature of the epidemic and the severity of the infection. In severe cases, petechial eruptions and hemorrhages under the skin are quite common in certain epidemics. The petechiæ may be so small as to be scarcely seen, or in some cases, especially in young children, the ecchymosis may cover areas as large as the palm of the hand, particularly in the acute malignant forms. A roseola like that in typhoid fever is not uncommon. Erythematous eruptions are quite common at the outset and give way to petechial forms. This is seen especially in children in whom an erythema may usher in the primary symptoms, to disappear in a few hours and be followed by a petechial eruption. Herpes are seen on the lips, alæ nasi, and different parts of the body. The writer has seen extensive herpes with bleb formation on one hand. These herpetic eruptions have nothing characteristic as to location. The contention that they differ from

the herpes in other diseases is scarcely confirmed by clinical observation, nor has examination of the contents revealed diplococci in the writer's investigations. In some epidemics herpes are more common than in others and they occur when pneumonia is not present, although they may occur when pneumonia is a complication. They are not pathognomonic of the disease. In some cases the herpes may be distinctly hemorrhagic.

Mental Condition.—It may be said in a general way that at the outset the intense headache gives way to sopor and subsequently to stupor. There is delirium of a mild type at first which may become noisy later on. If such patients are spoken to, however, they rouse from their stuporous condition and answer questions quite intelligently provided that the auditory apparatus has not been affected. In some cases there is distinct deafness, in which event it is impossible to come to any definite conclusion as to the mental state. In the acute cases which take a favorable course the patients come out of their delirious condition very much as in pneumonia and are quite bright, remaining so until the termination of convalescence, though other symptoms referable to the nervous system, such as rigidity, opisthotonos, and Kernig's sign may persist. In other cases the mental condition passes through the various stages of sopor, stupor and coma, from which they are never roused. In some, after having passed through the primary stage of stupor and recovered partial consciousness, convalescence is marred by a mental condition closely simulating idiocy. In this state the patient may continue for an indefinite time, finally recovering the normal condition or remaining idiotic.

The Nose and Throat.—In a large number of children in the epidemic of 1904–05 a coryza was present at the outset. In many cases this with conjunctivitis caused some confusion with measles. In quite a number of cases the tonsils and pharynx were markedly inflamed. In previous epidemics and in this present epidemic an examination of the discharges from the nose showed a diplococcus which in staining and cultural characteristics was identical with Weichselbaum's diplococcus. Shiff, Councilman, and Wright have found this diplococcus in the nasal secretions of the normal individual. Although the *Diplococcus catarrhalis* has a normal habitat in the nasal mucous membrane, there is no doubt that both in patients with meningitis and in those who have been in contact with such patients Weichselbaum's diplococcus may be found in the discharge from the nasal mucous membrane. Many children suffer from adenoids, and a nasal discharge from such causes must not be confused with the acute coryza mentioned before.

The Eyes.—Contrary to the generally accepted opinion we have found that examination of the fundus oculi in the majority of cases reveals no change in the optic papilla, although in quite a number there was dilatation of the veins and congestion without neuritis. In some cases there may be descending neuritis. In a group of 26 cases of meningitis of the tuberculous type neuritis was found in fully 77 per cent. It was either optic neuritis or papillitis with or without the presence of tubercles in the choroid. In those cases of cerebrospinal meningitis which recover, the damage to the eyesight must certainly vary in different epidemics. Blindness or definite changes in the fundus in those patients who have recovered in the recent epidemics in New York have been uncommon, although records of such cases are found in epidemics elsewhere. In the fatal cases an extension of the inflammation

along the optic nerve has been described. These changes may involve not only the nerve but the choroid, the vitreous and the structures of the globe. In various epidemics much confusion has been caused by records of eye lesions which evidently were not due to meningitis of the diplococcus type. In the epidemic of 1904–05 the writer saw many children in whom conjunctivitis was present, due apparently to affection of the nerves of sensation and loss of protection to the conjunctiva. The lesion is one of the fifth nerve. Other forms of conjunctivitis are due to the direct action of the *Diplococcus meningitidis*. Other eye lesions may be due to an extension of the inflammation along the optic nerve, causing neuritis and iridochoroiditis or even destruction of the globe. Keratitis is due to affection of the fifth nerve by direct extension (Councilman). The nerves of the muscular apparatus of the eyeball may be affected; thus paralysis of the abductor or oculomotor nerves may result. As to the simple absence or presence even of photophobia it is not possible to come to a definite conclusion. In this disease there is great hyperæsthesia and in some subjects this extends to the conjunctiva. The patients may lie with the eyes closed tightly and resist any attempt to open the lids. In others, especially young infants and children, no such symptom is noted.

The Ear.—The ear is more commonly involved in young subjects than in those later in life. In the majority of cases there is some redness of the drum. The younger the child the more apt is this to be the case. There may be otitis, with the formation of pus in which is found the *Diplococcus intracellularis*. In spite of assertions to the contrary, there is no case on record in which it has been proven that the disease was inaugurated by extension of primary inflammation of the ear to the meninges. In many patients who have recovered there is permanent deafness. This may complicate attacks which have been exceedingly mild and only lasted at the most a week, with complete recovery otherwise. In young children this complication may occur at the earliest stage, and is due to inflammation of the auditory nerve. Moos found that of 64 cases of meningitis fully 57 per cent. of those which recovered were deaf. Deafness may appear as early as the first day of the disease and as late as the fourth month of convalescence. It is possible that the abortive form of cerebrospinal meningitis is in many cases the direct cause of deafness.

The Blood.—In all cases there is a varying leukocytosis at the outset. This is of the polynuclear type and ranges from 20,000 to 55,000 to the cmm. exceeding 25,000 in fully 55 per cent. of cases. The lowest leukocyte count personally observed has been 11,000 to 12,000. This corresponds very closely to the observations of Osler. In the chronic form the leukocyte count may drop to normal and remain there for some length of time, in this way closely simulating what is seen in forms of tuberculous meningitis. Therefore, so far as the chronic forms of cerebrospinal meningitis are concerned, both in children and in adults, the leukocyte count is of no clinical value. The leukocytosis differs from that seen in tuberculous meningitis where the leukocytes rarely mount above 24,000 to 25,000, except in the pre-mortal state, when they may be 32,000. This is true both in children and in adults.

In the so-called basic cases in infants and children, the leukocyte count may range from 32,000 to 34,000, but toward the close of the disease when the temperature rises above normal it may fall as low as 9,000 to 10,000, in this latter respect resembling tuberculous meningitis. The majority of these do not recover, and are complicated with permanent hydrocephalus.

In the fatal cases in which fluid obtained by lumbar puncture is quite turbid or purulent the leukocyte count may be as high as 35,000 to 55,000, while in other fatal cases with a thick, turbid fluid obtained by lumbar puncture it will not exceed 23,000. Patients who have recovered showed a leukocyte count varying from 14,000 to 28,000, whereas during the course the count may have mounted as high as 45,000 even on the twenty-first day of the disease. Therefore, it can not be said that the prognosis as to a fatal issue can be made by means of the leukocyte count alone.

Kidneys.—In many cases there are evidences of a mild form of parenchymatous nephritis. There may be slight traces of albumin and a few casts. In some instances at the outset there is blood in the urine, with casts and albumin. These were patients in whom the petechiæ were prominent. In others, during the course there is polyuria, a patient of fourteen years of age voiding 60 ounces of urine in twenty-four hours, but these are uncommon. In a large percentage there are no symptoms referable to the kidneys.

Convulsions.—Convulsions are especially frequent at the onset, particularly in children. As a rule, they are not so frequent as in disease of the convexity of the brain alone or in leptomeningitis from various causes. In children the convulsions are not often repeated after the initial stage. Convulsions occurring in the course are of serious moment and point either to distension of the lateral ventricles of the brain or to pressure of fluid in the subarachnoid space both at the base and convexity.

Convulsions may supervene in patients who have run an ordinarily severe course and are apparently on the way to recovery. The temperature has begun to attempt to fall and is low. The pulse may be slow and then become rapid. The pupils may be dilated and there is a stupor. In these there may be signs of fluid in the ventricles. Convulsions in these patients are repeated daily and should warn us to intervene before a fatal issue. In such a patient seen recently there were all the signs of supervening hydrocephalus, and convulsions occurred daily. After lumbar puncture, the convulsions ceased and improvement was rapid. *Rigors* of a severe type may occur in the course of cases of an acute type. In such the exudate is slightly or markedly purulent.

Kernig's Sign.—This is probably the most discussed symptom or sign in connection with meningitis of recent times. Kernig, a physician of St. Petersburg, first described it in 1882 and published his results in 1884. He observed it in various forms of meningitis and confirmed the diagnosis at autopsy. The sign consists in an inability to extend the leg fully when the thigh is placed at right angles to the trunk. Kernig observed this sign when he attempted to set the patient at the edge of the bed and straighten the legs. He noticed that this was impossible, and following up his observation he found that this was the case in all forms of meningitis. Osler simplified the sign very much by showing that it may be elicited with the patient in the recumbent posture by placing the thigh at right angles to the trunk and then attempting to extend the leg on the thigh. Kernig not only found this sign in meningitis and considered it pathognomonic, but he observed it in the convalescence from the disease when the patient was up and walking about.

These observations have been confirmed with reservations. Kernig's sign is not pathognomonic of meningitis any more than rigidity of the neck. It is, however, very valuable and completes the picture of the disease. It is present in diseases of the most diverse nature where cerebral symptoms

are present and toxæmia is great. The writer has seen it repeatedly in pneumonia with meningism in children and it has been observed in adults in some diseases, such as typhoid fever.

It is important to recognize what is and what is not the Kernig sign, especially in meningitis. In some cases an attempt to straighten the leg on the thigh will be resisted at an angle of 135° and in others at an angle of 90°. It is therefore but fair to Kernig to include his sign between these two variations. Unfortunately this sign may be absent in malignant forms of cerebrospinal meningitis, especially in those with collapse symptoms, in which the patient a day or two after the onset is seized with a chill and goes into a condition of complete collapse, due, perhaps, to increase of fluid in the ventricles. In these patients the Kernig sign may be absent, although it may reappear on a subsequent day. It may be absent at the onset of an ordinary attack and appear after the disease has lasted a day or two. It is present in the majority of cases at some time in the course. As has been intimated, it may not be present at critical periods.

When Kernig's sign is present and an attempt is made to straighten the limb against resistance, there is intense pain, and a simulation of the Babinski reflex occurs at the time of the attempt to straighten the leg on the thigh against this resistance. The writer has seen no mention of this fact elsewhere.

During convalescence when the temperature remains normal for a variable length of time, the Kernig sign gradually loses its intensity, and as convalescence is established, as a rule, it completely disappears. Kernig's exceptional cases occurring during convalescence, when the patient was walking about, may be explained by the fact that these patients still had meningitis but in an unrecognizable form.

The cause of Kernig's sign has been a matter of much discussion. Roglet submits two causes. First, that it may be due to intraventricular pressure. This theory is supported by the fact, which the writer has confirmed, that the Kernig sign is not as marked after as before lumbar puncture. On the other hand, excessive ventricular pressure has, in the cases of collapse above mentioned, resulted in an entire disappearance of the sign. This causal agency, therefore, does not explain the sign completely. Another explanation is that the posterior spinal nerve roots are in a constant state of irritability and that there is, therefore, persistent tonic shortening of the muscular fiber which cannot completely straighten, and, hence, when an attempt is made to do so there is resistance. When the irritation of the posterior roots disappears the Kernig sign disappears.

As has been intimated, the Kernig sign is present in other forms of meningitis, but in tuberculous meningitis, especially in children, its presence is not so constant and in the cases studied by the writer it was absent in fully one-third. It is not to be relied on in very young infants in whom there is a muscular tonicity of both upper and lower extremities which is normal and becomes exaggerated on the onset of the least illness. Its occurrence in children below two years of age is variable for reasons which the writer cannot explain.

Babinski Reflex.—This was first studied in connection with chronic disease of the pyramidal tracts and lateral columns of the spinal cord. It is inconstant as a symptom of cerebrospinal meningitis, having been present in only 4 out of 25 cases, whereas in tuberculous cases its presence is more frequent, being absent in only 6 of 26 cases. Therefore, though it may not

be of value as a positive sign, its absence may be considered in the decision as to the nature of a meningitis.

The Reflexes.—In the majority of cases the skin and tendon reflexes are present in the early stages of the disease, but are apt to disappear in the rapidly malignant and fatal type, and in moribund cases.

Hyperæsthesia and Mental Irritability.—Very frequently, after the symptoms have set in, the patients are irritable, refuse to be comforted, start at the least sound, and lie on the side, this being most comfortable on account of the flexion of the arms, legs and trunk. Any attempt to disturb the patient is met with resistance. This is in marked contrast with other forms, especially the tuberculous, in which reaction to irritation is rather exceptional.

Tâche Cérébrale.—This is present in all the forms of cerebrospinal meningitis seen by the writer, both at the outset and in the course, but its value, especially in children, is rather lessened by the fact that it is present in most conditions in children in which the nervous system is affected by toxæmia and bacterial invasion.

Facial Paresis.—This is present in those forms, both in adults and in children, in which either at the outset or in the course the exudate and pressure symptoms are most pronounced at the base of the brain. During the epidemic of 1904–1905 these were not uncommon and simulated tuberculous meningitis with the exception that in the latter disease pareses are apt to supervene late in the affection, whereas in epidemic cerebrospinal meningitis pareses may supervene early in the course.

The grave significance of the facial paresis or paralysis in tuberculous meningitis cannot be applied to epidemic cerebrospinal meningitis, for they may disappear in the latter affection with convalescence.

Rigidity of the Neck.—Great stress has been laid on the presence or absence of rigidity of the neck both in adults and children as a pathognomonic sign in cerebrospinal meningitis. In those patients in whom the onset is foudroyant and in whom collapse occurs at the outset, neck rigidity, as well as Kernig's sign, may be absent. If the patient lives long enough to withstand the shock of the onset the rigidity may appear later with the Kernig sign. As a rule, neck rigidity is present in most cases either of mild or of marked severity, and with it there is mild or marked opisthotonos. It is in the posterior basic forms in young children that the rigidity and opisthotonos reach the height of development. According to Osler, rigidity of the neck is not usually present in the pneumococcus meningitis, but the writer has seen one patient in whom rigidity was present with opisthotonos. The rigidity and opisthotonos are so marked either early or in the course of the disease that any attempt to straighten the neck of the patient not only meets with resistance but causes pain. If at this time we observe the pupils we will see evidence of irritation, possibly of the sympathetic, as shown by marked dilatation of the pupils. Mydriasis which supervenes in any attempt to straighten the head, is a most valuable sign that the neck rigidity is due to irritation of the cervical nerve roots and thereby also the sympathetic fibers. This mydriasis is useful in differentiating rigidity of this kind from that which we so frequently find in gastro-enteritis and pneumonia in children.

Macewan's Sign.—Macewan has pointed out that in various forms of meningitis in children, especially of the tuberculous type, we obtain a hollow note on percussion over the anterior horn of the ventricle. That is, if the patient is caused to assume the upright position with the head inclined to one

side, percussion of the inferior frontal or parietal bone will give a tympanitic note. This more frequently obtains in tuberculous meningitis than in epidemic cerebrospinal meningitis.

In those cases of epidemic cerebrospinal meningitis in which hydrocephalus supervenes, both in younger and older children, the author has found that this hollow note is a very important guide to the presence of fluid in the ventricle. In cases of chronic hydrocephalus with increase of fluid in the ventricles a marked Macewan sign is always present. In a child below two years of age if there is marked rachitis a tympanitic note may be obtained in the manner described; such cases must be excluded in eliciting this sign in the study of cerebrospinal meningitis.

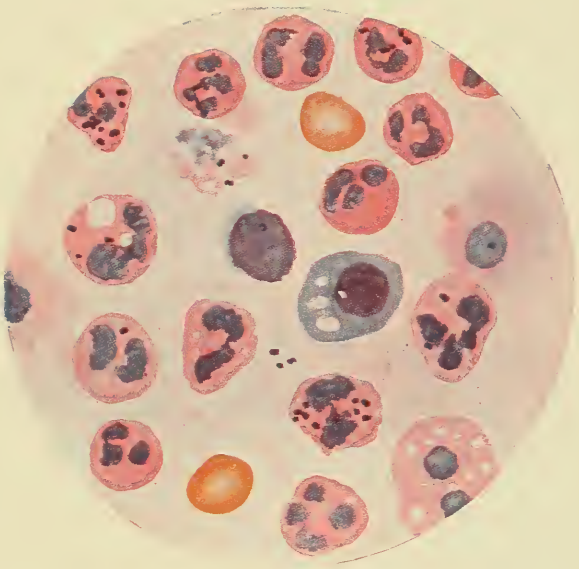
Lumbar Puncture.—The fluid obtained by lumbar puncture has been variously described and an attempt made to trace the connection between its physical characteristics and the course, duration and prognosis of the disease. The writer cannot agree with those views which take the physical characteristics of the puncture fluid as support for any of these data. At the outset the fluid may be quite turbid and purulent and the patients make a good recovery. The fluid at this time may be quite clear and the ultimate result just the contrary. A fluid which has been turbid at first may clear up subsequently, become quite clear, and after a week or two may again become turbid. An attempt has been made to explain the turbidity by reinvasion and regeneration of the microörganism. It certainly demonstrates a diminished resistance of the body to the invasion of the disease. In chronic or subacute cases of long duration, especially in children, the fluid finally becomes clear, and may be devoid of microörganisms or contain them in such sparse numbers as to be discovered only by the most painstaking measures. A culture from the subarachnoid fluid often gives a negative result and the fluid from the ventricles of the brain may contain diplococci.

The cytology of the fluid obtained by lumbar puncture is of great interest. It shows a preponderance of polynuclear leukocytes in a great majority of cases, the mononuclear leukocytes being present but in much diminished numbers. In a few cases seen by the writer, however, there were mononuclear elements present to a preponderating degree. (Plate XXII.) These are cases which have lasted some time and in which the disease has come to a standstill so far as active inflammatory processes are concerned, as seen especially in the chronic posterior basic cases, in which hydrocephalus has supervened. Here the mononuclear cells predominate as in tuberculous meningitis.

Bendix explains this variation by the fact that in chronic cases there is no longer an exudate but a transudate, and the course of the disease seems to substantiate this. Therefore, in acute cases a preponderance of polynuclear leukocytes in the puncture fluid is strong presumptive evidence against tuberculous meningitis.

In the puncture fluid we find the *Diplococcus meningitidis intracellularis* in the polynuclear leukocytes. It is situated mostly in the cells, in some instances seeming to pack the cell quite full, and in very rare cases it is found outside the cell body. In one case it was found in two successful punctures, then it was absent, while in the fourth puncture fluid it was present. Its presence or absence in the puncture fluid may not have any connection whatever with the clinical course, but be rather a matter of filtering through the fibrinous exudate. The writer has found the diplococcus a few hours after the onset and as late as the fifteenth week. In cases which have lasted over

PLATE XXII



Cover-glass Stain of the Sedimented Fluid Obtained by Lumbar Puncture in Epidemic Cerebrospinal Meningitis.

Polymorphonuclear cytology; vacuolization of the leukocytes and lymphocytes; peculiar conformation of the nuclei in cells; large cells resembling lymphocytes; Diplococcus meningitidis in the cell body of the leukocytes and also outside of the cell bodies in smaller numbers. Jena stain.

a few months it frequently disappears from the puncture fluid and is very difficult to demonstrate either by culture or cover-glass spread.

It may not be devoid of interest to note that in those cases in which the puncture fluid does not contain the diplococci or tubercle bacilli we may conclude rather in favor of the epidemic than the tuberculous type. The writer's experience rather substantiates the view that the presence of tubercle bacilli in the puncture fluid of tuberculous meningitis is quite constant and their detection depends very much upon patience and technique. In 14 cases diagnosed as tuberculous meningitis clinically, tubercle bacilli were found in 13. The search in some cases was quite prolonged and repeated, but they were present nevertheless. In tuberculous cases they are more abundant in the fluid removed after death, because it seems that the natural wave fluctuation present in the subarachnoid fluid during life tends to evenly distribute the bacilli through the subarachnoid space, whereas after death, sedimentation occurs.

In addition we find in the puncture fluid of epidemic cerebrospinal meningitis, mononuclear lymphocytes, with large nuclei, and a thin pale staining zone of cell body. Vacuolization of the leukocytes is not uncommon. In the polynuclear leukocytes the nuclei are irregular in shape and in various stages of division.

Complications.—These vary as to frequency and severity in different epidemics. In some epidemics, complications are rare, such as those connected with the eye, the ear, the skin, the joints, the lungs, the heart and the pericardium. In other epidemics these complications are quite frequent. This accounts for the variations in the descriptions of the disease.

The Eye.—In those patients who have recovered in the epidemics seen by the writer there have been few instances of blindness or severe, irreparable injury to the eyesight. In fatal cases, however, there have been a few in which panophthalmitis, with destruction of the globe, resulted.

The Ear.—Otitis in its various forms is a very frequent complication. In fact, in certain forms of the affection, especially in young children, English observers have advised early puncture of the drum even with slight symptoms of myringitis as a possible measure of relief. The otitis may be catarrhal or purulent and with or without mastoid complication, the latter being infrequent. Otitis is always secondary in cerebrospinal meningitis and there is no authentic case on record in which the infection began in the ear and from this spread to the meninges. The contrary is always true—the ear infections seems to be in direct extension from the brain, or an independent infection from the nose and throat. In quite a number of patients at the very outset or in the course, deafness supervenes without any lesion of the middle ear. In those there seems to be an affection of the auditory nerve apparatus. Some of these may improve in time, others remain permanently deaf.

The Skin.—Skin eruptions may scarcely be considered as complications, though subcutaneous abscesses have been mentioned in various epidemics. In some of these subcutaneous abscesses the diplococcus has been found.

Pericarditis.—Pericarditis seems to have been a complication in the fatal cases in the epidemic of 1904–1905. This may run its course and without any physical signs, even although these be searched for. In pericarditis few adhesions are found and the amount of effusion does not seem to be large. This would account in part for the fact that its diagnosis is difficult.

Pneumonia.—Pneumonia is not an uncommon complication. It may be caused by the *Diplococcus intracellularis* or by the pneumococcus. The course of the disease is severer than in uncomplicated cases. The presence of pneumonia means a fatal issue and the same may be said of pericarditis. In an epidemic, however, there are many cases of pneumonia which strongly simulate cerebrospinal meningitis and we should be extremely cautious in concluding that both are present. Sometimes it is almost an impossibility to come to a conclusion without lumbar puncture. We should not be too anxious to verify our suspicions in the presence of clinical symptoms which are not critical.

Joint Complications.—Councilman mentions the occurrence of arthritis and shows that it has been carefully observed by early writers, North, Welch, Jackson and Warren, at the beginning of the last century. Councilman, Mallory and Wright record 6 cases among 111 in the Boston epidemic. Osler has described arthritis complicating cerebrospinal fever and gives records of 2 cases in adults in which the wrists, hands, elbows, knees and other large and small joints, including the hip, were affected. The skin of the joints becomes red, brawny and diffusely erythematous for several inches above and below the affected joints. Over one knee which was affected there were purplish blotches. The pus withdrawn from one joint showed the meningococcus, and in 1 case at least the arthritis seemed to be a sequence of a species of meningococcus septicæmia, inasmuch as the meningococcus was isolated from the blood during life. This is the first case on record in which the meningococcus was found circulating in the blood in the living subject. The joint manifestations may be among the first symptoms of the disease.

During the epidemics of 1904 and 1905 in New York the writer saw several cases of joint affection, and in one similar to that of Osler the arthritis seemed to be one of the first symptoms. In the cases in children the arthritis never resulted in suppuration. The symptoms resembled more a mild attack of articular rheumatism, yielding promptly to ordinary treatment. In Osler's case, however, the joint affecti ns were more serious and were a manifestation of general sepsis; 1 patient died, the other, having begun with arthritis and fever, developed paraplegia and other serious symptoms. Joint affections in the course of cerebrospinal meningitis seem to be rather uncommon and to vary very much as t frequency and severity in different epidemics.

Hydrocephalus.—Among the interesting conditions met with in convalescence are those in which, the disease having run a moderately severe or mild course, the temperature having been normal for days and the patient apparently doing well, the mental condition becomes clouded. It is noticed that such patients no longer give attention to what is said to them and do not ask for nourishment. The pulse, having been slow, becomes slightly more frequent, the temperature may rise from subnormal, the pupils become dilated, there is a stupid stare, and the patients sleep most of the time. Percussion over the site of the horn of the ventricle as described by Macewan gives a hollow tympanitic note early in the condition. In such cases an accumulation has taken place in the ventricles of the brain and hydrocephalus has supervened. When this is relieved by lumbar puncture the patients seem to rouse themselves, the pupils return to normal size, the intelligence is awakened, as it were, but relapse may occur after several days, necessitating further interference. Such patients may make a good recovery, pass into a state of chronic hydrocephalus with idiocy, or a sudden fatal termination

may occur. In many of these patients there are intervening convulsions which cease on the relief of intraventricular pressure by lumbar puncture.

Age and Occurrence.—Prior to the year 1904 the writer had yearly 8 to 10 cases of cerebrospinal meningitis in his hospital service. These occurred independently of any epidemic. In the years 1904 and 1905, New York was visited by an epidemic of this disease and he is able to collect 119 cases, occurring in one hospital, both in children and in adults. The incidence as to age is as follows: Under one year, 25 cases; one to two years, 13 cases; two to four years, 17 cases; four to ten years, 32 cases; ten to fifteen years, 12 cases; fifteen to twenty years, 7 cases; twenty to twenty-five years, 1 case; twenty-five to thirty-five years, 4 cases; thirty-five to fifty years, 6 cases; and fifty to sixty years, 2 cases. The greatest frequency, in the author's material, has been in children below two years of age. This differs somewhat from Councilman's experience in Boston, in which the greatest frequency was at the ages of twenty-six and thirty years. The discrepancy may be accounted for in part by the fact of the difference in material. Whatever differences there may be in the statistics, it can be seen at a glance that the period between four and fifteen years of age, in which these statistics show 31 cases, is a frequent age of incidence. Between twenty and twenty-five years we had only 1 case. After the age of forty the disease is infrequent. This corresponds to most of the statistics available. The assertion of Councilman that the disease is rare under one year of age is not borne out by these statistics.

The mortality is greatest below one year of age. The youngest infant in these statistics was aged four months. Of the children below one year of age there were 27, among whom 20 died and in 3 the result was doubtful because they were discharged from the hospital in a condition of chronic hydrocephalus. These might very well be counted among the fatal cases inasmuch as there was very little hope of their recovery. Thus, in 27 cases below one year of age fully 23 either died or were discharged unimproved.

Between the ages of one and two years there were 13 cases, of which 9 died. Between two and four years there were 17 cases, of which 7 died. Between four and ten years there were 32 cases, of which 9 died. Between ten and fifteen years there were 12 cases, of which 6 died. In the years in which sporadic cases occurred there was a percentage mortality of 44 per cent., and in the epidemic years of 1904 and 1905 in the cases below fifteen years of age there was a combined mortality of 48 per cent. Among adults the greatest mortality seemed to fall between the ages of thirty-five and fifty years, in which period not a patient was saved in the hospital. Between the ages of fifteen and twenty years there were 7 cases with a mortality of 5. The mortality from twenty to sixty years was 12 out of 14 cases. The mortality seemed to be greatest, therefore, at the extremes of life,—between the ages of one and two years and between thirty-five and sixty years.

Epidemic cerebrospinal meningitis is a disease of infancy, childhood and adolescence. Its frequency diminishes after the twentieth year. Of a total of 120 cases, both among infants, children and adults, it would be unfair to estimate a general mortality, inasmuch as it has been seen the mortality varies at different periods of life. Of the total of 32 cases between the age of four and ten years there was a mortality of 9, or 28 per cent. In statistics which have preceded this article the greatest mortality in some epidemics has been 90 per cent., in others as low as 25 per cent. Thus, in judging of the efficacy of any

mode of treatment we have to reckon with the character and virulence of the epidemic and its mortality at various ages of life.

Diagnosis.—The diagnosis would seem to be quite a simple matter in the majority of cases, and such it is. The only other diseases which very closely simulate this affection are pneumonia, the cerebral forms of typhoid fever, and other forms of meningitis.

In epidemic cerebrospinal meningitis the onset is sudden in the vast majority. The patient is in apparent health when attacked with illness. The onset is with fever, headache and vomiting. In children convulsions are not uncommon. In the course of an epidemic an adult will suddenly be taken on the street, fall prostrated and unconscious; or he may complain of slight preceding headache and then become unconscious or have convulsions. In these cases the diagnosis is clear. In children, however, the onset occurring as it does in a great number of cases with symptoms referable to the gastro-intestinal tract, such as vomiting, diarrhœa, fever and abdominal pain, is not so suggestive. Conditions simulating very closely a mild attack of gastritis, which in twenty-four hours pass into a condition of collapse without any previous warning, are confusing. The pallor and the shock of the collapsed condition seem remarkable in view of the fact that the child may have been playing a few minutes previously. In such cases there are always evidences of some systemic infection and we must look for signs of the disease elsewhere. In a great many of these so-called foudroyant cases we find a few purpuric spots, which are telltale signs. In these cases there is nothing to aid in the diagnosis. The disease may have been of sudden onset with symptoms of gastro-enteritis and without rigidity or Kernig's sign to aid in the recognition.

The cerebral symptoms in some forms of typhoid fever which have their onset in an acute, abrupt manner have to be considered. The history is important and examination of the blood both for the Widal reaction and for the presence or absence of leukocytosis will aid in the diagnosis. An enlarged spleen may be present in cerebrospinal meningitis as well as in typhoid fever.

Cerebrospinal meningitis may be confounded with an ordinary attack of influenza or otitis. The ears should always be examined in doubtful cases or in unconscious patients with an unsatisfactory clinical history.

This form may be confounded with tuberculous meningitis or with that due to other causes. The pneumococcus meningitis may resemble it, although meningitis due to ear trouble fails to simulate the epidemic form in some of its most salient features, such as the onset, rigidity and opisthotonos. Some forms of streptococcus meningitis run their course without revealing any symptoms referable to the cerebrum until near the close, when a subdural collection of pus and a localized meningitis may become general. In such cases there is usually a history of previous ear trouble.

The tuberculous form may, in exceptional cases, simulate epidemic cerebrospinal meningitis. In tuberculous meningitis the onset is usually insidious. There is a prodromal period of at least a week or two in which the patient complains of indefinite malaise and in which symptoms are cumulative up to a certain period, after which they become pronounced. The leukocytes in tuberculous meningitis rarely mount above 20,000 to the cmm. except in the pre-mortal stage, whereas in epidemic cerebrospinal meningitis they are higher. In tuberculous meningitis the absence of reaction on the part of the patient to interference, the absence of hyperæsthesia, of neck

rigidity, as seen in cerebrospinal meningitis, of opisthotonos, both in children and in adults, aid in coming to a definite conclusion. The pareses seen in tuberculous meningitis referable to the affection of the cranial nerves at the base of the brain come on, as a rule, late in the affection, whereas in cerebrospinal meningitis they may be present at the onset or during the course. An examination of the fundus oculi may reveal choroid tubercles.

The whole mental picture in tuberculous meningitis is of the asthenic type, whereas it is of the sthenic type in the epidemic cerebrospinal form.

Treatment.—The treatment of cerebrospinal meningitis in the past proves to the mind of the writer the futility of drugs. The disease is a self-limited one, much like pneumonia, its duration practically uninfluenced by any mode of treatment, the patients recovering with or without complications independently of the effects of any known drug.

Modern treatment has been directed primarily toward an attempt to find a specific, which has failed. There is no serum as yet which will aid us in conquering the affection. This is, in a measure, due to the fact that the meningococcus does not generate toxins such as those of the bacillus of diphtheria. In the absence of any specific, the treatment is palliative and directed first toward the relief of the symptoms, such as pain, delirium, and fever, and to supporting nutrition.

It may be said that the reported success of certain remedies in particular epidemics is due to the mildness of those epidemics. We have nothing to cut short the disease. There is no drug, given early in the affection, which can abort it. Iodide of potassium given to tolerance has been administered but it is questionable whether it has any value. The pain and headache cannot be successfully relieved by any known remedy in every patient. Morphine seems to be directly harmful in the majority. It does not relieve the pain and in some cases makes them more restless than before. Bromide of potassium and chloral hydrate seem to be the only remedies which have given any relief so far as pain and headache are concerned. Veronal and pyramidon have been tried to allay the delirium, restlessness, and pain, with indifferent results. In fact in some cases the administration of these drugs appeared to be directly injurious.

The only measure which seems to relieve the vast majority, if it can be applied, is the hot bath. This was proposed by Concetti and has been tried by the writer for years with excellent results in relieving the restlessness and pain, and to a certain degree abating the fever. Patients can tolerate two full baths in the twenty-four hours, of a temperature of 107° to 110° F. for five or ten minutes. After such a bath the patients are not so restless and fall asleep for an hour or two, during which time there may be a pronounced perspiration.

The one modern measure which has raised hopes, only to cause disappointment, is lumbar puncture. The method of making lumbar puncture is that followed by Quincke. The patient is placed on the side and the puncture made between the fourth and fifth or third and fourth, lumbar vertebræ. The skin should be thoroughly cleaned and the needle boiled. In the adult the needle is entered 1 cm. to one side of the median line so as to pass between the laminæ; in the child the puncture is made directly in the median line. Adults, if restless, should be given chloroform but with children this is not necessary. The procedure can scarcely be said to be painful, although with these patients, being hyperæsthetic, the least touch gives

pain. Before the needle is entered, the spine is curved, the knees being held drawn up against the abdomen and the shoulders inclined toward the knees. In this way the spinous processes of the vertebræ become prominent and in children reveal the exact spot in which the needle should be entered, while in adults it places the ligaments on the stretch and allows the needle to pass more easily between the laminæ. In acute cases we may draw off from 30 to 50 cc. of fluid, according to the amount of tension or the turbidity of the fluid. If the fluid is very turbid the more drawn off the better as a matter of mechanical drainage. If the fluid is not so turbid we may repeat the puncture at some future day, and it is wise not to take more than 50 cc. at one sitting.

It has been proposed by Dana, in order to avoid the headache which follows puncture for a short time, to reinject a sterile serum. The writer advises against this in view of the fact that a sterile serum is very difficult to obtain and an imperfectly sterile serum is apt to do injury. In various epidemics, especially those in Spain, it has been proposed to inject drugs, such as the cyanide of mercury, or lysol in solutions of varying strength, into the subarachnoid space after a certain amount of fluid has been withdrawn. The writer has tried this method, especially with lysol solution, ½ to 1 per cent. or even stronger, and feels that it has not done any good, if it has not done harm. The simple injection of any fluid after withdrawal of the primary fluid would seem to be a severe test on the pressure conditions in the general nervous system and might be harmful. The good results which have been reported in various directions from the injection of lysol and drugs of all kinds must be looked on with great doubt, inasmuch as in every epidemic we see marvelous results not only with simple lumbar puncture, but sometimes when absolutely nothing has been done.

Indications for Puncture.—Clinicians have not, as yet, come to any definite conclusion as to the utility of, and indications for, lumbar puncture. It certainly seems to be indicated in those cases of sudden onset with symptoms of complete collapse. In these the collapse seems to be due to intraventricular pressure and for this lumbar puncture is a relief measure of the highest utility, inasmuch as such pressure is very dangerous. When lumbar puncture is made twenty-four hours after the onset, after such a period of collapse as has been described, the fluid sometimes spurts several feet. In such cases the relief of the intraventricular pressure is really a life-saving procedure.

Lumbar puncture seems to be indicated also in those cases where headache and delirium are excessive. The patient complains constantly of headache, has retraction of the head, opisthotonos and high fever. In such cases the intraventricular pressure seems to be great. In those cases in which, during convalescence, the patient suddenly develops symptoms of hydrocephalus, such as convulsions and stupor, dilatation of the pupils and subnormal temperature followed by a slight rise, and slow pulse followed by an increased rate, puncture should be done immediately and repeated at short intervals until the symptoms of hydrocephalus disappear.

In meningitis, the first result of intracranial pressure is an acute, subacute, or chronic distension of the ventricles of the brain with fluid, and it is the early detection of this fluid which gives the absolute indication to relieve distension by lumbar puncture. The mode of detecting acute hydrocephalus, whether caused by acute distension of the ventricles on the first day of a cerebrospinal meningitis, or during the slow, insidious onset of a tuberculous meningitis, is by percussion of the skull, as described elsewhere in this article

The writer considers percussion of the skull the only definite means of determining whether there is an increase of fluid in the ventricles or the subarachnoid space causing pressure effects, and therefore demanding immediate relief. There are cases of cerebrospinal meningitis with marked cerebral symptoms, in which puncture is scarcely indicated, because, though delirium, headache, hyperæsthesia, and sopor are present, we cannot demonstrate that there is any increase of fluid in the subarachnoid space and ventricles of the brain; therefore, lumbar puncture would not relieve pressure or symptoms.

The early idea of utilizing lumbar puncture as a method of *drainage*, by which a certain amount of purulent or suppurative fluid is removed from the inflamed district, seems a rather unscientific mode of treatment of meningitis of the meningococcus type. This disease is self-limited, and the physician should be ready to tide over critical periods, such as occur when intracranial pressure becomes extreme.

It may be asked how are we to know whether repeated puncture is necessary in a given patient? If, after lumbar puncture, there is an improvement in the headache and the patient becomes rational, we may wait a few days to see whether the previous symptoms return, or whether the patient continues to improve. Following this plan, after a puncture the objective symptoms may improve as well as the subjective ones, but the tympanitic note continues over the ventricle. If the patient is to improve, this tympanitic note gradually disappears, the symptoms improve, and in convalescence we no longer get signs of fluid in the ventricles. If the patient continues after a slight remission with the symptoms he had before puncture, we find that not only do the percussion signs of hydrocephalus continue, but there is a deepening of the objective symptoms, such as sopor, hyperæsthesia and rigidity, which gives the indication for a second puncture within twenty-four or forty-eight hours or more after the original puncture.

In this way we can do no harm if we are certain there is an excess of fluid in the ventricles. But, having relieved an acute hydrocephalus, if there is no return of symptoms, there is certainly nothing to be gained by a routine continuance of puncture in the face of improvement of the patient.

More difficult to treat are those cases which, in spite of repeated puncture, continue not only with the original symptoms of hydrocephalus, due to the re-accumulation of fluid, but in some, as we continue to puncture, the amount of fluid obtained diminishes with a diminution of the pressure, and we may attain to a point where there is little or no pressure at all as the fluid flows from the cannula. These are hopeless, because there is matting together of the parts at the base of the brain by exudate and a blocking up of the canals of Magendie and Mierjewski, preventing the fluid from the interior of the brain flowing into the subarachnoid space, thus into the subdural space of the cord, and externally. Lumbar puncture then fails to obtain the therapeutic end that we seek; not only the relief of the patient but the cure of the disease.

Patients with posterior basic meningitis, when the diagnosis is once established, should be treated energetically by repeated lumbar puncture, because the continuance of pressure in the subarachnoid space is directly detrimental and results inevitably in hydrocephalus or dilatation of the ventricles.

If lumbar puncture is carried out on the lines indicated above it is a humane and in some respects life-saving measure, but it must not be for-

gotten that we may carry a large number of patients with cerebrospinal meningitis through to recovery without lumbar puncture or with one primary puncture.

Nutrition.—One of the main effects noticed is that the general nutrition suffers from the very onset. The intense toxæmia, the fever, the delirium, the effects of the toxins and bacteria on the general nervous system, cause a rapid progressive emaciation. This is evident almost from the onset, and if the disease has lasted for a week the patient is seen to have palpably lost in weight. A patient in the condition of unconsciousness and delirium can be fed only at irregular intervals and this in short periods of time. If unconscious it is sometimes necessary to feed by gavage, which as a rule, is performed three times during the twenty-four hours. In this way enough nourishment can be given to the patient to maintain nutrition. Rectal alimentation is of very little value. The feeding will be still more difficult if there is vomiting, which usually does not seem to be caused by the ingestion of food, although food may be vomited when administered. In spite of vomiting it is well to insist on the continuous administration of liquid foods.

If the patients are not unconscious, even though they have fever, we may give solid diet. The tastes of the patient in this respect will guide the physician, who must not be afraid to give the most diverse articles, such as eggs, milk, soups, chopped meats, toasted bread, and cereals of all kinds. In children the appetite is especially capricious and unless we give the food in small quantities and at frequent intervals the patients literally starve themselves. In those cases the nurse must be ever ready with water, milk and soups in small quantities, in this way embracing every opportunity to maintain nutrition. A careful record should be kept of the amounts given, as a guide that the patient is properly fed and at the same time not overfed.

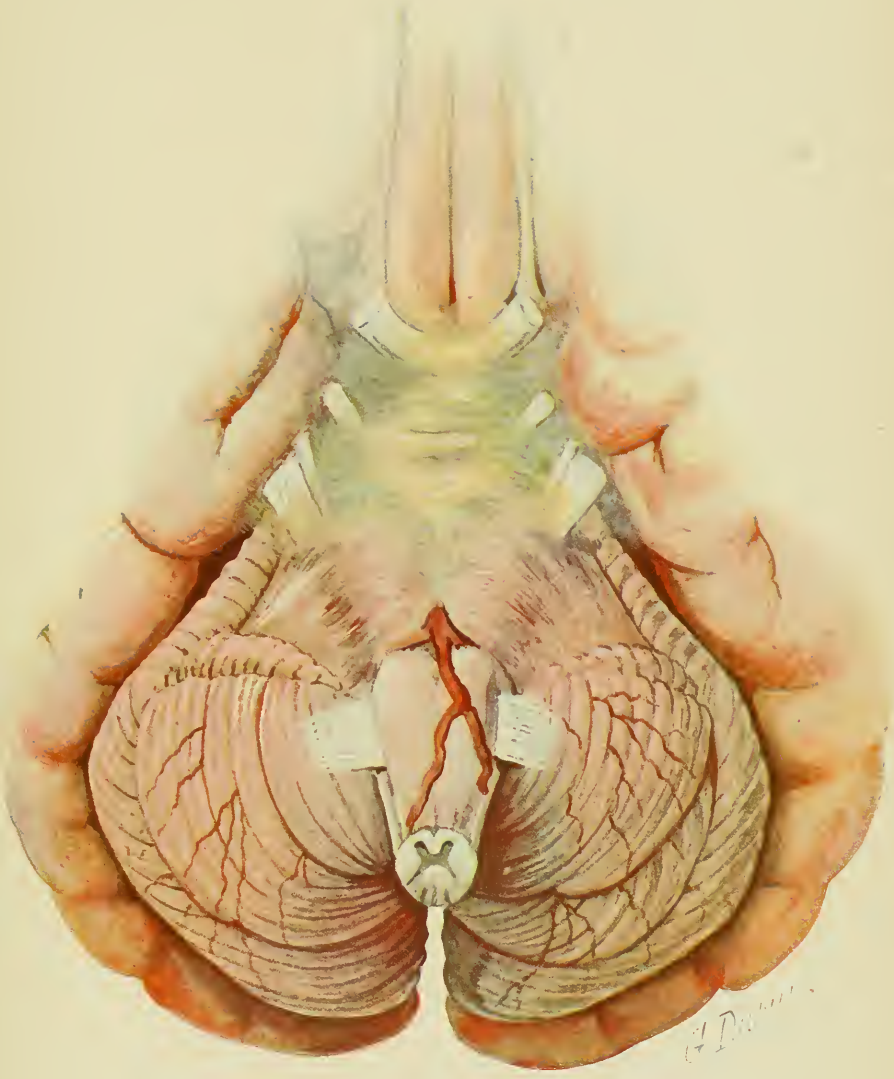
Fever.—The fever requires very little treatment. As a rule, the highest range of temperature lasts but an hour, sometimes even less, and there is a natural fall in the temperature, so that no strenuous effort need be made to treat the fever directly.

During convalescence the patients are weak and complain of stiffness and pains in the extremities. In such cases hot baths and judicious massage are particularly useful. Rough handling is painful, a fact which should be impressed upon the nurse. Gentle massage of the extremities once a day strengthens the patient and reduces the pain and stiffness in the muscles and joints.

The complications, such as those connected with the eye and ear, cannot, unfortunately, be relieved by any form of treatment known. During convalescence some patients, especially children, have a peculiar gait. They are very unsteady and walk very much as do the subjects of Ménière's disease. This condition may improve and gradually disappear of its own accord. It is seen especially in patients who are completely or partially deaf, and in whom there has been no affection of the middle ear. The otologists hold out very little encouragement in these cases as to the ultimate return of hearing, but hearing sometimes returns to a certain extent without any treatment. In other cases the hearing seems to have been permanently lost.

The joint affections are treated on general principles. If the joint is painful and swollen it may be wrapped in cotton moistened with methyl salicylate, and salicylate of sodium given. If there is suppuration of a joint surgical treatment is indicated.

PLATE XXIII



Posterior Basic Meningitis. (Gee, Barlow, and Still.)
Author's case in an infant.

POSTERIOR BASIC MENINGITIS.

Posterior basic meningitis may be said to be the form which acute cerebrospinal meningitis of the epidemic type takes in children below two years of age. In these subjects the peculiar conformation of the brain at the base seems to predispose to the development of this symptom complex. It is not seen, as a rule, in older subjects, and for a time was thought to be a form of meningitis *sui generis*, due to various causes. It is quite evident now, however, from observations during epidemics of cerebrospinal meningitis and of sporadic cases, that the same etiological factor obtains as in older subjects, and that the youth of the subject, the susceptibility of the tissues, and possibly the conformation of the parts, tend to the development of certain symptoms.

This peculiar form of meningitis was first described by Gee and Barlow, in 1878. They described 25 cases, and the essential feature of all was "the holding back of the head." In fact they called the disease cervical opisthotonos. They also laid stress on the fact that in other forms of meningitis and in tuberculous meningitis this peculiar symptom of head retraction was only exceptional, whereas in this form of the disease it was a constant symptom. In some of their cases the onset was gradual, in others sudden. In those cases in which the onset was sudden the opisthotonos alone, or accompanied by fever, vomiting, and muscular rigidity, seemed to be characteristic. The associated symptoms included rigidity of the limbs and convulsions during the course, which was chronic and particularly fatal inasmuch as only 3 of their patients recovered.

Similar cases have been described by Carr, and Still called attention to this affection in 1898 in a report of the postmortem findings in 8 cases of the 49 that he had collected. In these 8 cases he discovered, either in the ventricles or in the fluid withdrawn from the subarachnoid space, the *Diplococcus intracellularis* of Weichselbaum, although at the time Still was not absolutely certain of the identity of his microörganism with that of Weichselbaum. Nuttall subsequently proved the identity of the two organisms.

Morbid Anatomy.—The pathology has been clearly described by Lee and Barlow and by Still. The inflammation seems to limit itself to the posterior part of the base of the brain as the primary seat of inflammation in most cases. From this region the inflammation spreads down the cord to a varying degree, upward along the line of the ventricles, and forward along the base as far as the optic commissure and tips of the temporo-sphenoidal lobes; or the inflammation may begin in the transverse fissure and choroid plexuses. (Plate XXIII.) At an early stage the products of inflammation though circumscribed may be suppurative; later on they may become absorbed, but meningitis with adhesions results. These adhesions may unite the cerebellum and medulla, obliterate the foramen of Magendie and the fourth ventricle. This, it is thought, gives rise to fluid in the ventricle and consequent hydrocephalus.

In some the fluid found in the ventricles is clear, in others it contains flakes of fibrin and pus. In the latter cases the ependyma will be found to be thickened. In one of the writer's cases the surface of the brain was pale and the convolutions were flattened and at the base was a small amount of organized exudate. The floor of the fourth ventricle was bulging and ready to burst. The foramen of Magendie was almost obliterated.

In some of these cases the viscera are normal, in others the lungs are found collapsed. The thymus may be enlarged and show symptoms of congestion. The heart muscle may be pale and show parenchymatous changes. The spleen may be slightly enlarged. The liver may be fatty. The stomach may show a few hemorrhagic areas on the fundus and there may be enteritis in the intestine. The mesenteric nodes of the intestine may be slightly enlarged.

In this form of meningitis there are few complications, whereas in 15 cases of suppurative meningitis there were complications such as pleurisy or necrosis of the petrous portion of the temporal bone. In some cases described by Still there was a mucopurulent secretion in the middle ear, but in none was there evidence of mastoid disease or extension to the brain or meninges.

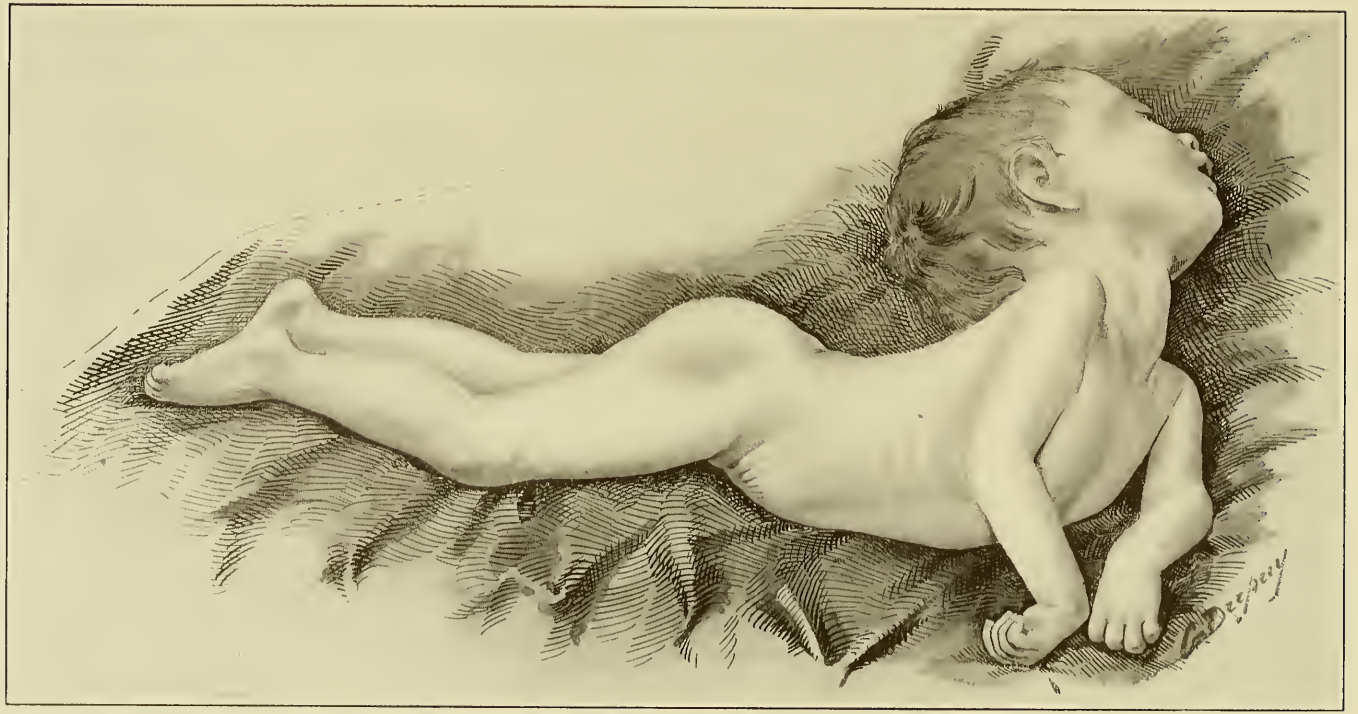
In some of those cases which are fatal within six weeks, postmortem examination shows lymph at the base of the brain and cord. In those which die after three or four months there is hydrocephalus, with a thickening of the pia mater and arachnoid, with adhesions between the cerebellum and medulla and slight thickening of the pia covering the temporal or the temporo-sphenoidal lobes. The cord may present hemorrhages in the cervical, mid-dorsal and lumbar regions.

During the epidemics of cerebrospinal meningitis of 1904 and 1905 the writer has seen quite a number of children below two years of age in whom the disease took this peculiar form. Of 8 cases of posterior basic meningitis occurring during the epidemic of 1904 the ages ranged from four months to three years, and 1 was five years of age. The ages were four months, six months, nine months, three years, two years, and five years, respectively. The history was negative as regards syphilis or tuberculosis in all. There may or may not be a history of previous ear trouble or exanthemata.

Symptoms.—The mode of onset, speaking only of cases below two years of age, which correspond accurately to the picture given by Gee, Barlow, and Still, was gradual in only 1 case. In the others the onset was sudden. The beginning of the disease may have simulated tonsillitis or an ordinary attack of gastro-enteritis, in that the child was taken with fever, vomiting, then with convulsions in some cases, and these convulsions may have been repeated daily for some weeks. After the disease had lasted for several days it was noticed that the head was retracted and the neck rigid. In other cases after the initial fever and vomiting the child became stupid and then the mother noticed that the fever continued and that the child was blind. In such cases the child may take nourishment or reject it by vomiting.

When fully developed the picture of the disease is quite characteristic. The children are somewhat emaciated, lie quietly, seldom crying out, the head is retracted, there is more or less opisthotonos, the upper and lower limbs may be adducted, the forearm flexed on the arm and the thighs on the abdomen, and the fingers flexed. In some cases they present the picture in the upper extremities seen in tetany—the so-called driving position of the hands. In other cases the lower extremities are extended and cannot be flexed, although the upper extremities may be strongly flexed. The foot may be strongly extended on the leg and the toes on the plantar surface of the foot, in this way resembling tetany. The body is bent backward, the head assuming an angle of nearly 90° with the spine. At times this opisthotonos and tetany relax and the spastic phenomena are not so apparent. (Plate XXIV.) As soon as disturbed, however, or if the surface of the back is rubbed, the patients assume the position of extreme opisthotonos. In others, in addition, there is a ten-

PLATE XXIV



Posterior Basic Meningitis. Characteristic position of the head and extremities. Child aged fourteen months.

dency to cross the legs. In some there are purposeless movements of the upper extremities in a sort of arc in front of the face. If the fontanelles are still open they bulge, and the sutures, in some cases in which hydrocephalus has supervened, are pressed apart by accumulation of fluid in the ventricles. In some there are spasmodic contractions of the muscles of respiration to such extent as to cause a peculiar hissing sound in the larynx and extreme bulging of the thorax. In other cases there is strabismus. As a rule the heart, liver and spleen show no changes. In all cases emaciation is extreme and the abdomen is retracted and rigid.

The temperature at first is raised two, three or four degrees above the normal. After some time the temperature may fall to normal or for days range between normal and one degree above normal, in this way simulating tuberculous meningitis. In others, after some weeks, without any apparent cause the temperature will mount from normal to 106° F. or over, and then fall to normal or subnormal daily, to rise again. These great excursions of temperature do not last very long and seem to be due possibly to cerebral pressure, for after puncture there is not any exacerbation of infection in the form of a new accession of diplococci in the puncture fluid. On the contrary, in those cases the fluid was sterile.

The condition of the fundus of the eye is interesting. In most patients below two years of age there is no change in the fundus, no neuritis, contrary to what is seen in tuberculous cases in the majority of which there is change in the fundus. In all cases seen by the writer there was disturbance of the circulation, such as tâche cérébrale or evanescent erythema due to vasomotor paresis. Kernig's sign is of very little value for the reason that the patients lie in the spastic or flexed position and the thighs cannot be flexed on the abdomen. The so-called Babinski reflex is absent in most of these cases.

The Blood.—In most cases there is a leukocytosis ranging from 14,000 to 30,000. In many cases, however, the leukocytes may not mount above 10,000 to 14,000, in this way simulating tuberculous meningitis very closely.

Of special interest is the character of the fluid obtained by lumbar puncture. In many chronic cases it is not possible to obtain fluid by lumbar puncture, inasmuch as the canal of Magendie may be closed by adhesions. In those in which fluid is obtained it is found to be sterile in some instances, while in others it contains the *Diplococcus intracellularis*. Although in most cases the diplococcus may be found at the outset of the disease, later on it seems to disappear from the fluid or be present in very small numbers. Although the fluid may show a preponderance of polynuclear leukocytes, later on when hydrocephalus supervenes mononuclear leukocytes may predominate.

The cause of hydrocephalus in posterior basic meningitis has been the subject of much discussion. It has been contended by English writers that a narrowing of the canal of Magendie, with an accumulation of fluid in the ventricles and their consequent dilatation, results in a permanent transudate in this locality. This, however, would not explain the great number of cases in which hydrocephalus exists with a patent canal of Magendie. Another explanation is that the vessels of the plexus of Galen becoming thrombosed, their walls thickened and inflamed, and circulation is retarded, thus causing a transudate into the ventricles.

Neither of these theories explains the particular symptoms in posterior basic meningitis. Given a child below two years of age attacked by cerebro-

spinal meningitis we still are at a loss to explain why, in the majority of cases, hydrocephalus follows. Aside from the cases of posterior basic meningitis, whose etiology has been dilated upon, the author has been fortunate in encountering a case of purely basic meningitis posterior in type in which the etiology was not that of the diplococcus of Weichselbaum but a pure streptococcus complicating a pneumonia. This proves that in older children we may have posterior basic meningitis pure and simple, the exudate being only at the base of the brain and of exactly similar nature to the form of the disease just described, but due to streptococcus infection secondary to pneumonia.

Thus there are two forms of basic meningitis. First, primary, caused by the *Diplococcus intracellularis* of Weichselbaum and either epidemic or sporadic. This is the type of the disease described by Still. The second form occurs in older children and the symptoms in no way resemble those described by Still. There is no drawing back of the head, or opisthotonos; the symptoms are obscure until near the close. The characteristic symptoms of the first form are absent, but in addition to the stupor and symptoms of meningeal involvement we have, late in the disease, facial pareses, paralysis of the ocular muscles, slight rigidity of the neck, and Kernig's sign pointing toward involvement of the brain, especially at the base.

The author wishes to emphasize that the cases of posterior basic meningitis of the type described by Gee, Barlow, Lees, and Still may occur in epidemics and are due to the same essential cause as the form of the disease in older children and adults. In fact it would appear that in the majority of children attacked by cerebrospinal meningitis below the age of two years, both in epidemics and sporadic instances, the disease takes the form described by these authors.

Treatment.—It has been proposed lately to interfere surgically in these cases. The skull having been trephined, one horn of the ventricle is opened and a drain of catgut is fixed in it, connecting this with the subarachnoid space, thus making the ventricular and subarachnoid spaces one. Pressure can thus be relieved by a general outflow of fluid. We have no statistics as yet of the success of this but it is difficult to see how anything else than the substitution of an external for an internal hydrocephalus is attained.

German authors (Bôkai) have published several cases of apparent cure of hydrocephalus following meningitis (posterior basic) by repeated lumbar puncture, extending over prolonged periods, such as six months or a year. The writer has never succeeded in attaining any results by this method when hydrocephalus has once been established.

The treatment is most unsatisfactory. In a child below two years of age with meningitis, the prognosis of itself is bad; if, added to this, the disease is progressive, we know of no remedy which will stay its course. It has appeared to the writer that in these cases lumbar puncture would attain its ideal as a palliative measure if instituted early enough and repeated often. Its utilization must be directed especially to the prevention of the subsequent hydrocephalus, which seems hopeless when once established. Therefore, although a patient is apparently doing well, we should not hesitate to puncture repeatedly in order that intraventricular pressure may not permanently dilate the ventricles. The peculiar structure of the brain in these young subjects seems to invite the hopeless sequel of hydrocephalus.

CHAPTER XX.

ERYSIPELAS (ST. ANTHONY'S FIRE, THE ROSE).

By JAMES M. ANDERS, M.D., LL.D.

Definition.—Erysipelas is an inflammatory disease of the skin due to a streptococcus infection, and characterized clinically by a tendency to spread through the lymphatics, by intermittent fever, and by moderate prostration. It has an average duration of fourteen days. Erysipelas occurs both in an endemic and epidemic form.

Historical.—Erysipelas was known from remote antiquity. Fairly accurate clinical accounts may be found in the works of Hippocrates on "Epidemics," and to him, and later to Celsus, we owe our first acquaintance with surgical erysipelas. Hippocrates also distinguished with a fair degree of accuracy idiopathic from traumatic erysipelas. The clinical course was described by the Arabian physicians and by Greek and Roman authors. The older writers, as well as those of the middle ages, however, confused erysipelas with a variety of other morbid processes, more especially of the skin, lungs, and uterus. Galen, who first drew the distinctions between erysipelas and phlegmon, attributed causative influences to the weather, but held that the effect on the blood of certain changes in the biliary secretion was the principal causative factor. The bilious theory of the origin of erysipelas held sway until Henle (1840) called attention to the probable etiological role played by organisms. Later, Volkmann, Huter, Tillmanns, as well as Billroth and Ehrlich, supported the microörganic theory of the disease by experimental investigations; but it remained for Fehleisen to prove that the definitive cause of erysipelas is a streptococcus.

Epidemics of erysipelas of which we have accurate reports occurred in France as early as 1750, and outbreaks of a most virulent type nearly a century later (1842–43), both in Europe and America, have been carefully recorded. It is probable that, as stated by Haser, the epidemic of smallpox which occurred in the United States in 1699 was accompanied by erysipelas. Among excellent accounts by American physicians are those of Drake, Sutton, Dexter, Peebles, and others. These epidemics greatly advanced our knowledge of the disease, although their erysipelatous character may be seriously doubted in some cases at least, notably the great scourge or the so-called "typhoid erysipelas" which originated in Canada in 1841 and spread in a southeasterly direction over the entire United States. At the end of the eighteenth and beginning of the nineteenth centuries, hospital epidemics were described by Wells, of London, and later (1840) at the Hôtel Dieu, in Montpelier, by Serre, and similar outbreaks by subsequent writers.

The epidemics were formerly attributed to errors of hygiene and overcrowding, but this failed to explain repeated outbreaks in hospitals, educational institutions, almshouses, and hospital ships, despite the most rigid cleanliness. The observations of Ferguson, Ollier, and others, afforded convincing proof that erysipelas can make for itself a permanent habitation

in institutions and municipalities, giving rise to the endemic or sporadic form, and, under favorable local conditions, the cases may multiply into epidemics.

Upon the general acceptance of the discovery of the cause of erysipelas, further speculations, which so often led the older writers into hopeless confusion, were happily obviated. Clinical observations have been greatly facilitated by the absolute bacteriological proof of the specificity of the disease.

Etiology.—The exciting cause is the *Streptococcus erysipelatis* (Fehleisen), but it has been proven that this organism is identical with the *Streptococcus pyogenes*. Petruschky has shown that streptococci derived from non-erysipelatous morbid processes were powerful to produce a typical erysipelas. V. Eiselsberg, E. Fränkel, Widal, and others, had previously furnished absolute proof by experiments upon animals that the separate identity of the *Streptococcus erysipelatis* cannot be reliably established. The streptococci of erysipelas flourish in all sorts of culture-media, are very minute although variable in size, and usually assume the form of a serpent or chain-forming coccus of Cohn. They are found principally in the minute lymphatics of the skin, and rarely, also, in the capillary bloodvessels, and are especially abundant as well as active near the advancing edge of the erysipelatous area. They are rarely found in the general circulation, and in blood-serum disappear by the action of the phagocytes. Intra-uterine infection has occurred in exceptional instances. The general symptoms of the disease are due principally to the presence of toxins circulating in the blood.

There is abundant proof that the streptococci multiply outside of the body; they offer great resistance to external influences. This is confirmed by the repeated epidemic outbreaks in hospitals and institutions, resulting from local favoring conditions. The occurrence of an institutional epidemic, however, involves the coincident presence of individual predisposition. Kiliani, Kruse, and other writers, direct attention to commencing erysipelas of the mucous membrane of the nose. These cases are not spontaneous, and the habit of "boring the finger into the nose" will explain many cases of facial erysipelas. The process does not always begin at the site of the integumental lesion, the streptococci traversing the lymphatics for some distance before implantation occurs.

The streptococci cause diseases other than erysipelas and all of these exhibit the typical fever-curve of streptococcus infection. Inoculation with streptococci derived from a patient caused typical erysipelas in man. This experiment by Fehleisen and other investigators furnished the final proof of the causative role of the streptococcus.

The *mode of infection* is clear; it may occur from the inoculation of wounds (traumatic erysipelas) or from accidental inoculation in the vicinity of the nose and mouth (spontaneous or facial erysipelas). The next most favored point of selection is the leg; thus out of 586 cases of the idiopathic variety 517, or 88.2 per cent., were facial; 50, or 8.5 per cent., occurred on the legs and feet.[1] Other parts of the body surface, as the hands or scrotum, are rarely the site of infection. Acute coryza may precede the attack (*e.g.*, in 13 out of 301 cases), and in such cases slight even microscopic lesions of the Schneiderian mucous membranes probably exist and serve as an infection atrium.

[1] Anders: *Journal of the American Medical Association*, July 22, 1893.

Mode of Conveyance.—Erysipelas is inoculable and less commonly contagious, although as a general rule the virus is not highly virulent and therefore is probably conveyed but a short distance. The organism has been collected from the air of rooms and wards occupied by erysipelas patients. The poison is also transferred for a longer or shorter distance by fomites, by instruments, and the unclean hands of the physician.

Predisposing Causes.—1. *Season.*—Erysipelas occurs most frequently during the cold, damp months of spring and autumn. The writer[1] has shown by an analysis of 2,010 cases that 50 per cent. occur during the months of February, March, April, and May, and 15.9 per cent. during April alone. These figures also indicated a rise in incidence, month by month, with slightly varying ratio from August to April, after which there is a rapid decline until the minimum number is reached, in August. It was noted that a low barometer and mean relative humidity invariably correspond with the annual period of maximum prevalence. Per contra, the highest percentage of relative humidity in the atmosphere corresponds with the months affording the fewest cases.

2. *Age and Sex.*—From an analysis of 1,894 cases the writer found that 25.8 per cent. occurred between the ages of twenty and thirty years. The disease is rare before the tenth year of life, if we except newly-born infants, whose great liability is well established. Of the writer's series (1,894 cases) 15 per cent. occurred before the age of twenty, while after fifty years of age the incidence rapidly decreased.

The sex was noted in 1,767 cases, and the result showed a greater prevalence among males than females. On the other hand, Frickhinger found in nearly 700 cases from v. Ziemssen's clinic that 26.91 per cent. were males, while 73.09 per cent. were females. The balance of statistical evidence indicates the more frequent occurrence of erysipelas among women as compared with men.

3. *Previous Attacks.*—Individual predisposition is shown by the frequency of recurrences, although the importance of this factor has probably been overestimated. In 450 instances studied by the writer, prior attacks were noted in 39, or 8.6 per cent. It was observed that recurrences affected principally patients afflicted with protracted suppuration, and especially those suffering from catarrhal lesions of the nares accompanied with slight fissures about the nose and mouth—lesions that furnish a path of ingress to the streptococcus. In menstrual erysipelas the recurrences may take place at intervals of four to five weeks' duration.

4. *Family predisposition* exercises an influence in rare instances.

5. *Antecedent Affections.*—The important etiological role played by lesions of the nasal mucosa has been emphasized. The marked predisposing influence of certain chronic diseases, such as phthisis, nephritis, organic heart disease, and alcoholism, has been definitely shown.

6. *Slight Abrasions, Fissures, and Traumatism.*—Minute, even invisible, lesions of the skin and mucous membrane of the nose, or the cutaneous surface of the face or ear, invite infection by furnishing a portal of entry. Women after delivery, and subjects of surgical operations, are peculiarly susceptible for an identical reason. In the same manner a deeply seated focus of irritation, *e. g.*, chronic suppuration and necrosis of the bones, may be an underlying cause for repeated outbursts of erysipelas.

[1] *Journal of the American Medical Association*, July 22, 1893.

7. *Antihygienic Surroundings.*—In hospitals and institutions in which the sanitary conditions are conspicuously faulty, frequent outbreaks of the disease occur. It may, however, appear in new institutions under the most desirable environment.

Special Pathology.—Erysipelas is a simple inflammation involving the skin, subcutaneous tissues, and less commonly the mucous surfaces. When the process reaches the subcutaneous connective tissue suppuration as a rule follows; this belongs to the more virulent forms of the affection. Osler in one case traced an extension of the inflammation from the face along the fifth nerve to the meninges, "where an acute meningitis and thrombosis of the lateral sinus were excited." It is believed that extension inward from the skull by still other routes to the meninges may also rarely occur. The various viscera may present complications usually of a septic character, and visceral infarctions are not very uncommon. Osler states that of 23 cases of malignant endocarditis 3 were secondary to erysipelas. Simple endocarditis, affecting the aortic and mitral segments, and pericarditis may be noted. Out of a total of 1,810 cases (with 119 deaths) the postmortem lesions of pneumonia were observed in 4 instances, acute nephritis in 3, pleuritis in 1, œdema of the larynx in 2, and widespread abscess formation in 8. The streptococci are found in the lymph spaces near the margin of the advancing inflammation, while beyond the confines of the spreading inflammation, they occupy the lymph vessels, where they are attacked and may be finally overpowered by the leukocytes.

Symptoms.—Incubation.—This varies in duration and ranges usually from three to seven or ten days. During this period prodromata may appear; they are anorexia, headache, restlessness, angina with cough, malaise, and slight pyrexia. These symptoms last from a few hours to as many days.

Stage of Invasion.—The symptoms are (*a*) general, and (*b*) local. The disease is usually ushered in with repeated fits of chilliness or a distinct rigor, vomiting, and a rapid rise of temperature to 104° to 105° F. The temperature usually reaches its maximum, 105° to 106.8° F., on the evening of the third day. After a few days of continued fever the temperature-curve becomes irregular, with marked noctural remissions often merging into a distinctly remittent or even an intermittent type. At the end of one week the temperature may decline by crisis, or, after a more protracted febrile period, by lysis. As the result of complications, and in erysipelas migrans, a prolonged and irregular fever-curve is the rule.

In the majority a direct correspondence between the temperature-curve and the severity of the localized inflammation exists, although, rarely, violent and extensive local symptoms may be associated with a moderate elevation of temperature, particularly in adynamic forms of the disease or such as occur in aged and previously debilitated subjects. An evening rise after a period of normal temperature points to a rekindling of the inflammation, or a relapse. The writer has been able to confirm the observations of DaCosta, Strümpell, and others, that the cutaneous inflammation in erysipelas (particulary erysipelas migrans) may advance to a slight extent even after the temperature has returned to normal. Following a severe attack the temperature may be subnormal for a few days.

The pulse is accelerated, of good volume, and more or less compressible. The constitutional depression may be great, more particularly in alcoholics.

A polymorphonuclear leukocytosis paralleling the violence of the infection occurs in this disease, but streptococci have not been found in the blood. The *nervous symptoms* vary in intensity. Headache and restlessness, with nocturnal delirium, particularly in the severer forms, are commonly present. In the drunkard, delirium tremens may suddenly supervene. The *urine* shows the usual febrile characters, including slight albuminuria in many cases at least. Acute nephritis occurs rarely. Kirkbride found leucin and tyrosin in the urine in one case, which indicates a marked disturbance of metabolism.

The tongue becomes heavily furred, and nausea and vomiting are not uncommon. There is constipation as a rule, but in some patients at an advanced stage diarrhœa may occur. Enlargement of the lymphatic glands is found occasionally in the neighborhood of the erysipelatous area. The spleen is moderately swollen as a rule.

Local Symptoms.—In facial erysipelas the starting point is usually the bridge of the nose, the affected part feeling hot, tense, painful, and sensitive to touch. Almost immediately a small circumscribed area becomes red, swollen, and shining, and the inflammation then spreads laterally in the direction of the ear, over one or both cheeks, and also upward, but rarely implicating the tip of the nose. The point of election may occasionally be on the ear, the cheek, or the hairy scalp, and erysipelas is said to have a preference for the right cheek. The erysipelatous zone may embrace not only the entire face and ears, but eventually the scalp and even the neck as well. Separating the affected from the unaffected skin there is a sharp line of demarcation—an elevated brawny ridge presenting a wholly irregular outline. While the inflammation is meandering, beyond its borders small red streaks and spots that grow in size until they become confluent may be observed. Certain natural integumental folds, as the nasolabial and border of the hairy scalp serve to arrest further extension in many cases. The nostrils may be obstructed and the patient limited to mouth breathing. In a fully developed case the swollen face, tumefaction of the eyelids, great enlargement of the ears (better marked on one side than on the other as a rule), and swollen scalp, tend to produce marked distortion of the features often to an extent beyond possible recognition.

Several sub-varieties of the local inflammatory process are recognized. Thus the inflammation may spread to the trunk, the arms, and even to the legs, when it is known as *erysipelas migrans*. In such instances the parts first affected may exhibit a normal condition of the skin before the local process ceases to spread elsewhere. In some cases the epidermal layer becomes elevated over circumscribed areas presenting smaller or larger vesicles or bullæ—*erysipelas vesiculosum*. The larger blebs may be attacked by suppuration, giving rise to so-called *erysipelas pustulosum*. In exceptional instances necrosis or gangrene occurs—*erysipelas gangrenosum*. When the subcutaneous tissue becomes involved the local manifestations are violent, the fever continues high though irregular in type, and prostration is marked; this is spoken of as *phlegmonous erysipelas*. The local process may extend in depth until the intermuscular spaces and even the periosteum and bones are invaded. The condition often leads to other varieties mentioned above—*e.g.*, *erysipelas gangrenosum* and *pustulosum*. In the new-born the disease may attack the umbilical cord (*erysipelas neonatorum*). From the navel the inflammation may spread to the thighs and genitals. There is fever, and the

patient falls into fatal collapse from the sixth to the tenth day. Certain complications, as gangrene or suppuration, may arise. Erysipelas may recur at longer or shorter intervals, usually in the same locality—*relapsing erysipelas*. This chronic form of the disease is commonly due to some deep-seated focus of suppuration. Desquamation attends the subsidence of the erysipelatous process, and the complexion becomes more delicate than before the attack.

Erysipelas of the Mucous Membrane.—From the skin the erysipelas may extend to the pharynx, thence through the Eustachian tube to the middle ear and downward to the larynx, trachea, and even to the bronchi. This may lead to œdema of the glottis. The disease may also attack the mucous surfaces primarily, and this form is ushered in by constitutional and local symptoms similar in character to those met with in cutaneous erysipelas. When it begins in the nasal mucous membrane or throat the local phenomena are not characteristic until, as commonly occurs, secondary facial erysipelas supervenes. There is violent pain, redness, and decided parenchymatous swelling, with a sharply defined outline of the affected mucous membrane. While extension to the skin usually takes place from the nose it may occur either through the external ear or the nasal duct, though less commonly. The submaxillary lymphatic glands show enlargement and are tender. There are cases which begin as primary erysipelas of the larynx, although this is rare. The local changes may pursue the course of a primary independent disease, or extension downward through the trachea to the bronchi or even air-vesicles may occur. The sudden development of stenosis of the larynx with death from suffocation has been noted.

Complications and Sequelæ.—An analysis of 1,674 cases by the writer with particular reference to complications gave the following result: Abscess 105, arthritis 20, delirium tremens 10, lobar pneumonia, active delirium, phlebitis, pleurisy, each 7, acute nephritis 6, synovitis and diarrhœa each 5, tonsillitis 3, catarrhal pneumonia, otitis media, œdema of the larynx, acute bronchitis, each 2. In a series of 140 cases Lenhartz observed abscesses 9 times (6.1 per cent.). In 4 of these 9 cases the abscess was located in the eyelid. Abscesses occur most commonly upon the head, but also in other parts, may be single or multiple, and while as a rule subcutaneous abscesses are moderate in extent, they may rarely attain to a massive size. Hoffa has observed a purulent arthritis of the knee, and purulent meningitis is an exceptional complication. The swelling of the lymphatic glands may proceed to suppuration; this is usually in association with subcutaneous abscesses or gangrene of the skin. Extensive cutaneous gangrene, however, is rare. The *Sanitary Reports of the Royal Prussian Army* embrace 5,606 cases of erysipelas with but 8 cases of severe gangrenous inflammation. Widespread abscess formation may lead to generalized sepsis with fatal exhaustion, and the condition may be due to a mixed infection.

Gubler has described endocarditis in the course of erysipelas, and since then Sir Dyce Duckworth, Hall White, and others, have reported similar cases.

Soft, blowing, functional murmurs may be noted and should be differentiated from organic murmurs. The writer has observed arrhythmia due to myocardial weakness from the action of the toxin on the muscular structure of the heart. The same symptom may be occasioned by disturbed innervation. In addition to lobar pneumonia, aspiration bronchopneumonia

may occasionally appear. The pneumonia which complicates erysipelas, especially in the wandering form, may be an actual erysipelatous or streptococcus pneumonia. Lenhartz, in a series of 140 cases, observed acute nephritis 7 times, or in 4.7 per cent.—a higher percentage than in the writer's figures. A chronic otitis media or chronic nephritis may date from an attack of erysipelas. Conversely, erysipelas is reputed to be curative of a variety of diseases, more particularly eczema, lupus, rheumatism, carcinoma, and sarcoma. After erysipelas the hair often falls out, but is usually replaced.

Relapses are not so common as recurrences, but are nevertheless of comparatively frequent occurrence. Out of 476 cases collected by the writer relapses occurred in 54—*i.e.*, 11.3 per cent.;—in 1 of these 5 relapses occurred; in 2 others, 4. The relapse may appear after an afebrile intermission of but one or two days, although commonly the interval is three to five days. It may be of short duration and yet accompanied by rather violent symptoms. In another group of cases, to which Frickhinger has directed attention, the relapse may be afebrile and yet the cutaneous area involved may be as large as in the primary attack. On the other hand, DaCosta has called attention to curious irregular exacerbations of the fever during convalescence from the primary attack without any aggravation of the exanthem.

Diagnosis.—This is not difficult when the eruption is fully developed and typical. The brawny, ridge-like, advancing margin of the inflammatory process forms a well-defined line of demarcation between the healthy and diseased skin, and is one of the distinctive characteristics. The appearance, seat, and behavior, particularly the tendency to spread, form marked peculiarities. Of less diagnostic importance, although of considerable value, are the acuteness and severity of the constitutional disturbance and the enlargment of lymphatic glands in the neighborhood, as well as the variable course due to the part affected and the presence or absence of complications. A bacteriological diagnosis is often possible by examining the pus or secretion from the nasopharynx, which shows the presence of the streptococcus.

The diagnosis of erysipelas of the mucous membranes is exceedingly difficult, and, as a rule, possible only when preceded or followed by cutaneous erysipelas. Under these circumstances redness and swelling with marked pain would justify a reasonably certain diagnosis. Primary erysipelas of the mucous membranes is characterized principally by similar local symptoms developing acutely and either preceded or accompanied by a rigor. The constitutional features are the same as in cutaneous erysipelas, and painful enlargements of the lymphatic glands in the neighborhood may also be observed.

Differential Diagnosis.—*Acute eczema* has been confused with erysipelas, but lacks the fever, marked swelling, peculiarly raised advancing border, and mode of progression, which characterize the latter disease. Moreover, eczema is accompanied by intense itching. The same points of difference, coupled with a longer course, enable a ready elimination of *chronic erythematous eczema.*

Eczema nodosum is characterized by nodosities which have their favorite seat in the vicinity of the articulations. *Erythema* is unattended with local heat, swelling, pain, and fever. *Urticaria* has been confounded, but appears in the form of pale-red circular wheals in successive crops (often fleeting within a few hours) and with intense pruritus. The affected areas are gener-

ally scattered over the entire body. *Malignant pustule,* affecting the nose, was mistaken for erysipelas in a patient observed by the writer. Although erysipelas bears a superficial resemblance to this disease in the early stages, the swelling of anthrax is exceedingly firm and presents the characteristic central, depressed scar. A positive discrimination, however, demands a bacteriological and microscopic examination.

Prognosis.—Three main considerations form the basis of prognosis in the individual case: (*a*) The severity of the type of the disease, (*b*) the presence or absence of complications, and (*c*) the circumstances directly connected with the patient himself. As to the first, it may be stated that erysipelas rarely assumes a malignant form. More or less severe types are sometimes observed as indicated by the degree of fever, its duration, the cardiac rate, and nervous phenomena—delirium, stupor. When the disease occurs in drunkards, delirium tremens may arise and death occur.

Of the complications, those fraught with greatest danger are excessive suppuration, pneumonia (lobar or lobular), acute nephritis, gangrene, phlebitis, pleurisy, pyæmia, and œdema of the larynx. On the other hand, acute arthritis, while comparatively common, is without effect upon the morbidity. The average duration in typical cases under forty years of age is fourteen days, but complications materially lengthen the course. They are rarely the direct cause of death if we exclude lobar pneumonia, acute nephritis, and delirium tremens.

As stated above, the condition of and circumstances connected with the individual are important. In the first place, the outlook grows graver (after the fifth year) in proportion to the age, and this is especially true after forty-five years. Thus the analysis of 1,810 cases indicated that age has a decisive influence upon the mortality after the forty-fifth year, this becoming still more pronounced after the sixtieth year. These figures gave a general mortality rate of 6.57 per cent. for hospital cases and 4.16 per cent. for those from private practice; in persons under forty years the death-rate was only 3.5 per cent., in those over seventy years 46 per cent., and the traumatic cases gave a mortality of 14.5 per cent. Of 2,663 deaths due to erysipelas (*United States Census Report*), the death-rate per 100,000 inhabitants was as follows: Under five years, 31.34; five to fifteen years, 0.81; fifteen to forty-five years, 2.80; forty-five to sixty-five years, 8.88; sixty-five and over, 38.55 (Rodman). With reference to age, it is important to recollect that a greater proportion of children under five years and of old people perish than of the middle-aged and adolescent.

The preëxistence of certain chronic affections, notably pulmonary tuberculosis, chronic nephritis, and organic cardiac diseases, not only increase susceptibility but also augment the mortality as much as 25 per cent. On the whole the mortality rate is low, and when death occurs it is usually attributable to exhaustion or asthenia.

Treatment.—This may be considered under four heads: (1) Prophylaxis, (2) diet, (3) constitutional treatment, and (4) local measures.

1. **Prophylaxis.**—This has reference not only to measures limiting the spread of the disease, but also to the prevention of a relapse. It is probable that relapses are sometimes due to auto-infection, or a reinfection from without; and to obviate this danger frequent changes of the body-linen and removal to another room during convalescence are advisable. In persons who have suffered from previous attacks a recurrence may be prevented by

treatment of some of the predisposing conditions, such as chronic nasal catarrh, necrosis of nasal bones, chronic leg ulcers, and the like.

The antiseptic treatment of wounds led to a marked decrease in the cases of erysipelas; but strict isolation of the disease from the injured, and, more particularly, operation cases, is the most efficient preventive. It is advisable to isolate all patients with erysipelas, since there may be transmission by contact from the sick to persons apparently free from wounds, fissures, suppuration, or other lesions. Gerhard reports an interesting case which occurred in an orderly who had nursed an erysipelatous patient and was attacked by pharyngitis. Immediately after a subsidence of the sore throat a secondary facial erysipelas appeared; it had propagated itself through the right side of the nose and attacked the cheek. It is obvious that since the diagnosis is not made until the eruption has appeared on the cutaneous surface, transmission may occur before the erysipelatous character of the disease is recognized.

Admission of erysipelatous patients to hospitals should be refused, except to institutions provided with an isolation building, special physicians, nurses, and other employees. When erysipelas appears in a hospital that has no isolation wards, the patient should be completely isolated and the same rules rigidly followed as in other infectious diseases. The physician should wear rubber gloves, which can be readily sterilized and thus prevent transmission to other patients.

The serious significance of erysipelas in the new-born makes prevention of great importance. Puerperal women should be guarded from all danger of exposure. Besides strict isolation, scrupulous care of the skin of the entire body is a necessity. Bathing with a boric-acid wash (3 per cent.) not less than thrice daily, so as to disinfect the desquamating epidermis is strongly advised.

2. **Diet.**—A tendency to exhaustion is manifested in the more protracted cases, hence alimentation must be generous. If the temperature be high, the diet should be restricted to liquids given in definite amounts at stated intervals. It should consist especially of milk predigested or diluted with simple water, barley water, or lime water, but not with aërated waters. Albuminized milk, albumin water, animal broths, beef-tea, and bouillon, may be added during the febrile stage. In persons over fifty years of age and in those exhausted by previous chronic disease, an appropriate dietary is of the first importance and may be the means of abridging an otherwise much protracted attack. Rectal alimentation should be used if the stomach is upset, but should be discontinued as soon as milk and other liquids are well borne by the stomach. Under special circumstances both methods of feeding may be required temporarily to maintain strength. When convalescence begins, and in the lighter cases throughout the attack, pulled bread, toast, well-boiled rice, and eggs, may be allowed. As convalescence advances other solid foods of the more digestible kinds are to be given.

The value of an appropriate diet is scarcely appreciated by the general profession. Unquestionably, minute attention to the details of alimentation during the primary attack may be preventive of a relapse. It should be definitely understood that appropriate liberal feeding is of greater service than any of the forms of medicinal treatment.

3. **Constitutional Treatment.**—Direct personal experience and theoretical considerations have led to the belief that correct, vigorous feeding often

renders the use of stimulants wholly unnecessary. When, however, the pulse becomes rapid and feeble, the action of the heart weak, faint, and irregular, with or without the presence of a dry, brown tongue, stimulants are indicated. Whisky and brandy are best, the dose being governed by the effect upon the circulatory system. If alcohol fails, others may be given simultaneously. The judicious use of strychnine has been most serviceable in the hands of the writer, in doses of moderate size, at first gr. $\frac{1}{40}$ every fourth hour, to be gradually increased until a favorable effect is produced. Should urgent symptoms arise, either suddenly or gradually, strychnine may be administered hypodermically until the blood tension has been restored, after which its use by mouth may be resumed. Digitalis may also become an invaluable aid during the advanced stages, either alone or combined with strychnine; it may be given in doses ranging from 5 to 15♏ of the tincture, every third or fourth hour. As a temporary stimulant, adrenalin chloride is helpful and should be administered hypodermically (♏iij to v of a 1 to 1,000 solution). Under similar circumstances saline injections given subcutaneously or intravenously increase the blood pressure; they may be repeated at intervals of six to eight hours as occasion demands. Effective doses of diffusible stimulants, as champagne or aromatic spirits of ammonia, are also useful during circulatory depression. If the renal secretion is scanty or diminished, more particularly if albuminuria or acute nephritis be present, nitroglycerine should be regularly given. Finally, while arterial stimulants are required in some, they are not needed in the majority of cases.

The extent to which erysipelas is amenable to medical treatment depends on the conception one has formed as to the nature of the affection. It is important to recollect that we have to deal with a bacillary toxæmia. Consequently it becomes necessary to induce elimination. The bowels should be moved gently but regularly by fractional doses of calomel, followed by the daily administration of a mild saline, as sodium phosphate. The sweat glands may be stimulated by sponging the surface with tepid water or water as hot as can be borne; this may be repeated twice or thrice daily. There is a special method of treatment having for its object the induction of copious sweating and thus to abort the attack, which will be referred to hereafter. Large quantities of water should be regularly and systematically given, to which potassium bicarbonate or acetate may be added in severe cases. It is especially important to attend carefully to the details connected with elimination.

Attempts have been and are continually being made with various kinds of specific treatment, but these have failed to justify their use. The writer's best results have been obtained with the employment of certain remedies, notably iron and quinine in combination. The tincture of the chloride of iron, first recommended by Hamilton Bell in 1851, has been extensively used by English authorities, and was looked upon by the older clinicians as a truly sovereign remedy. Other preparatians of iron are probably equally efficacious, and while experience has proven the undoubted value of iron, it does not deserve to rank as a specific. In 74 cases of erysipelas treated by the tincture of the chloride of iron alone, the average daily quantity being 1 dram in divided doses, at the Pennsylvania Hospital, Philadelphia, by Lewis, DaCosta, Longstreth, Meigs, and others, the death-rate was 4 per cent.[1]

[1]Anders: "The Treatment of Erysipelas," *Therapeutic Gazette,* July 16, 1894.

The dose of the tincture of iron should not be less than 10 to 30♏, repeated every second or third hour, according to the severity of the attack. The effect of iron is much enhanced by associating with it quinine, which may be given separately in capsules or milk. In England this remedy enjoys a wider reputation than iron, as the result of the well-known experiments of Binz. The daily dose of quinine should range from 16 to 30 gr.; its use may be confined to instances in which the temperature reaches 103° F. or over, and usually in uncomplicated cases the nocturnal remissions became decidedly greater and the course of the disease appeared to be somewhat abridged. After long experience the writer is of the firm conviction that this combined method of internal treatment merits a trial in all suitable cases.

Reference has been made to the method of treating erysipelas by inducing copious sweatings, with a view to aborting the disease; it was first used by the late J. M. DaCosta at the Pennsylvania Hospital, Philadelphia. The writer has no experience in the use of pilocarpine in this affection and would advise care and caution on account of its depressing effect upon the heart. In 1881, M. Hallopeau suggested the combined local and internal use of sodium salicylate. Quite brilliant results have been reported from this remedy.

Numerous antiseptic agents have been recommended, but in not a single instance have they earned a lasting reputation. Marmorek, Knorr, Chantemesse, and others, have successfully immunized certain animals (rabbit, donkey, horse) by the subcutaneous injection of highly virulent streptococcus cultures. Instances of its successful use as a curative agent have been reported by Andre, Robinson, and others, but experience with Marmorek's serum has on the whole given contradictory and unsatisfactory results. The effect of the serum lasts over two days, but it has to be repeated at forty-eight hour intervals to obtain all its advantages.

Certain symptoms may require treatment. Antipyretics have little or no influence on the fever and are strongly contra-indicated on account of their depressing effect. High fever can be met by the application of ice-bags, cold sponging, or gradually cooled baths. The effect of quinine is to reduce temperature and more particularly to lengthen the nocturnal remissions. Pain, insomnia, and active delirium, are favorably modified by the use of hyoscine hydrobromate (gr. $\frac{1}{200}$ to $\frac{1}{100}$, hypodermically). This is contra-indicated in the presence of feeble heart action. The following may be used: Sodium bromide gr. v (0.324 gm.) every two hours, or gr. xx to xxx (1.2 to 2.0 gm.) at night; potassium bromide gr. x (0.6 gm.), and tincture of cannabis indica ♏x (0.6 cc.), in combination. Occasionally local discomfort and pain are troublesome features and are best combated by morphia, gr. $\frac{1}{8}$, hypodermically. The treatment of *complications* must be conducted as they arise. In meningitis local bloodletting and lumbar puncture should be considered.

4. **Local Measures.**—These have always held a prominent place. In three different series, making a total of 247 cases, the remedies most commonly employed locally were elm, lead-water and laudanum, carbolic acid (1 to 40) injected subcutaneously, zinc oxide, mercuric-chloride solution, and ichthyol ointment with lanolin. One of the indications is the exclusion of air with a view to inhibiting the growth and development of the organism, which can be best accomplished by the use of carbolized vaseline or carbolized oil. To Hüter belongs the credit of introducing the method of injecting

carbolic acid (1 to 40). The object is to check the spread of the inflammatory process by inserting the needle at numerous points just beyond the inflamed margin. It is especially serviceable in erysipelas migrans. Whether in the usual facial erysipelas it has any advantages over other modes of treatment may be doubted. The local use of a solution of mercuric chloride has been followed by the writer in hospital and private practice with encouraging results. More recently it has been recommended to scarify the affected area and then apply a solution of mercuric chloride (1 to 4,000). Assuming that the streptococcus occupies mainly the superficial channels of the corium, it follows that a bactericidal effect by the mercuric-chloride solution may be reasonably expected.

Ichthyol has been extensively used by Nussbaum, Fessler, Klein, and others, but that it exerts a specific effect lacks clinical support. Sarcinelli has found that erysipelas of the face healed rapidly under application of a thin cotton face mask impregnated with .25 to .5 per 1,000 solution of corrosive sublimate, alternating every two hours with another similar mask impregnated with a 3 per 1,000 salicylate solution. Agents whose influence is partly mechanical and partly chemical (astringent) have also been employed. Of these collodion and ichthyol-collodion (10 to 50 per cent.) are painted in a tolerably thick layer not only over the erysipelatous area but also over the surrounding healthy skin for 2 or 3 centimeters. MacLennan advocates a saturated solution of picric acid as a local remedy; he finds that it arrests the spread of the morbid process and relieves the local discomfort and burning better than ichthyol and other agents.

CHAPTER XXI.

LOBAR PNEUMONIA.[1]

By JOHN H. MUSSER, M. D.,

AND

GEORGE WILLIAM NORRIS, M. D.

Synonyms.—Peripneumonia; peripneumonia vera—Sydenham (as opposed to peripneumonia notha—obstruction of the lungs by heavy, viscid, pituitous matter); pneumonic fever—Huxham; croupous pneumonia; lobar pneumonia; pneumonitis; sthenic pneumonia. German: Lungenentzündung; croupöse Pneumonie. French: pneumonie lobaire; fluxion de la poitrine. Popular terms: lung fever; in North Germany, Fleier, which according to Jürgensen is a corruption of the word pleuritis.

Historical.—Lobar pneumonia, owing to the striking and characteristic clinical picture which it so often presents, has been known since the earliest times not only to the medical profession but to the laity as well. It is prominently mentioned and discussed in the writings of Hippocrates, although at this time there was much confusion and no differentiation between pneumonia, pleuritis and other acute thoracic diseases. Four centuries later Aretæus, Celsus and Thenison made further progress in the study of the disease. According to Curt Sprengels, Diokles of Karystus, one of the oldest writers, pointed out the difference in the pathology of pneumonia and pleuritis. Although mentioned and described by Galen, Cælius Aurelianus, Ætius, Alexander Trallianus, Rhazes, Avicenna and others, no great advance was made until the days when physicians refused to be bound by the previously invincible rules of custom and precedent, and began to think and investigate for themselves. This era began about the time of Harvey, Sydenham and Malpighi.

The relation between the clinical manifestation of pneumonia and consolidation of the lungs was pointed out by Morgagni, while Baillie described the morbid process as "hepatization." Further important studies were made by Laennec, Cruveilhier, and Rokitansky. The diagnosis of pneumonia, based upon the physical signs, is of course to be accredited to Auenbrugger and Laennec. Addison showed that the inflammatory

[1]Before writing the present article on croupous pneumonia the authors endeavored to collect from the entire literature all the statistics which were available. The statements made are based upon the study of thousands of cases reported by observers in different parts of the world. The total number of cases available for the investigation of a given subject of course varied greatly, since the classification of different authors varied, as did also the individual subjects upon which data were furnished. The "collected cases" referred to in the text therefore represent the results of our compilation from our own cases, as well as those of the literature in general. Owing to lack of space it has been impossible to reproduce the exhaustive tables giving an itemized account of the cases reported by different observers, or to include the references.

exudate was intravesicular and not interstitial, while to Rokitansky belongs the credit of differentiating between lobar and lobular varieties. Joerg,[1] Bailly, Legendre and Bichat did much to distinguish the various forms of atelectasis or defective expansion from inflammatory processes.

Occurrence.—The actual frequency of pneumonia as compared with all internal diseases is given by different observers as follows: Baeck, for England, France, and Germany, 6.4 per cent.; von Ziemssen, 3 per cent.; Aufrecht, 4 per cent.; Kiel, 1865–82, 3.6 per cent.; Tübingen, 1873–86, 2.6 per cent.; Vienna, 2.6 per cent.; Berlin, 2.5 per cent.; Townsend and Coolidge (Boston), 1 to 3.5 per cent. Wells, among 400,000 hospital admissions, found 2 to 2.5 per cent. due to pneumonia; Aufrecht, 4.1 per cent. among 36,540; Jürgensen, 5 per cent. among 3,993. Ziemssen has estimated that pneumonia represents about 3 per cent. of all, and 6 to 7 per cent. of internal diseases. According to Fraenkel it represented from 12.7 to 6.7 per cent. of all diseases in the Saxon and Würtemburg army corps during twenty years,—1878 to 1898. O. Müller states that this percentage is steadily decreasing by virtue of better hygienic precautions.

In the United States during the census year of 1890, over 9 per cent. of all deaths were due to pneumonia, in 1900, over 10.5 per cent. Comparing the city with the country districts, the last-named census shows the proportion of the mortality per 100,000 of the population to be 233.1 and 135.9, respectively. In England and Wales in 1899 the death-rate from pneumonia was 125.5 per 100,000.

The health statistics of Chicago seem to indicate that there has been a very marked increase in the number of cases of pneumonia in that city, one-eighth of all deaths being due to this cause, 46 per cent. more than from all other contagious diseases combined, the mortality from tuberculosis being thus exceeded by one-third. During the last forty years the mortality from pneumonia has increased from 4.4 to 19.95 per 10,000 inhabitants. The last census report of the United States shows that the most marked increase in pneumonia during the last ten years has been in the first three years of life and in the aged.

On the other hand a number of papers have been written to show that these statistics are erroneous, and that the apparent increase has resulted from faulty returns of the cause of death, and the misinterpretation of figures. It may be conservatively stated, however, that the frequency of pneumonia is at least not diminishing, and that the number of deaths caused by this disease is appalling.

The two following charts, representing the frequency and mortality of pneumonia in the Allgemeine Krankenhaus in Vienna and the Glasgow Royal Infirmary indicate graphically the yearly variation in prevalence and the constantly increasing frequency of the disease.

The increasing prevalence of pneumonia in Philadelphia is shown in the chart taken from Wells'[2] article. The solid line indicates the deaths per 1,000 of population, the dotted line the percentage of the total deaths.

[1] A more complete study of the historical aspect is to be found in Jürgensen's classical work in *Ziemssen's Encyclopedia;* also in Wells' article, *Journal of the American Medical Association*, February 9, 1889; and Neumann, *Krankheiten des Menschen*, 2d Ed., I, p. 151.

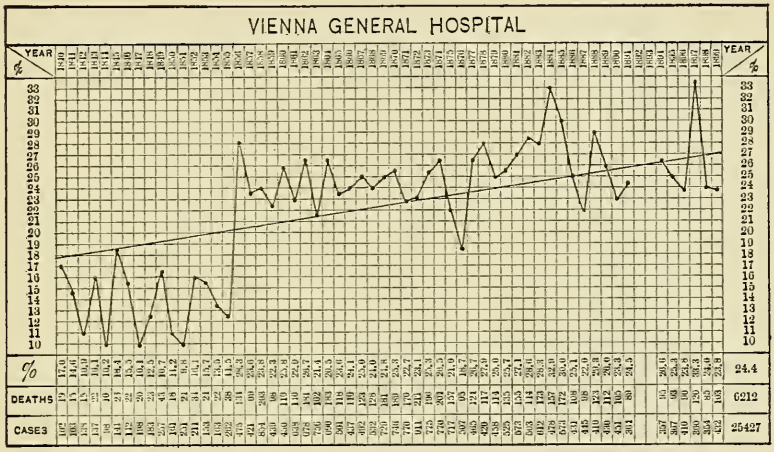
[2] *Journal of the American Medical Association*, February 4, 1905.

THE ETIOLOGY OF LOBAR PNEUMONIA.

Predisposition.—Factors favoring the occurrence of pneumonia.

I. General Factors.—(*a*) *Increased Virulence of the Microörganism.*—There can be no doubt that the virulence of given strains of the pneumococcus varies greatly from time to time. This fact no one who has seen many cases of pneumonia, or who is familiar with the literature of the subject can doubt. The organism apparently tends to increase in virulence with each passage through a human subject, just as it tends to decrease in virulence when cultivated artificially. These facts are particularly brought out when we investigate the various epidemic outbreaks of the disease. At such times

FIG. 62.



it has frequently been noted that in a given household the most robust member is the last to succumb, in other words he had sufficient immunity to withstand infection, until the virulence of the pneumococcus had been enhanced by the successive passage through the less resistant members of the family.

(*b*) *Annual, Seasonal and Monthly Curves.*—It has been satisfactorily demonstrated by nearly all statistics that the disease exhibits very marked exacerbations during certain years. The incidence in various months is shown by the following statistics of 34,587 cases collected bv the writers:

MENSAL FREQUENCY.

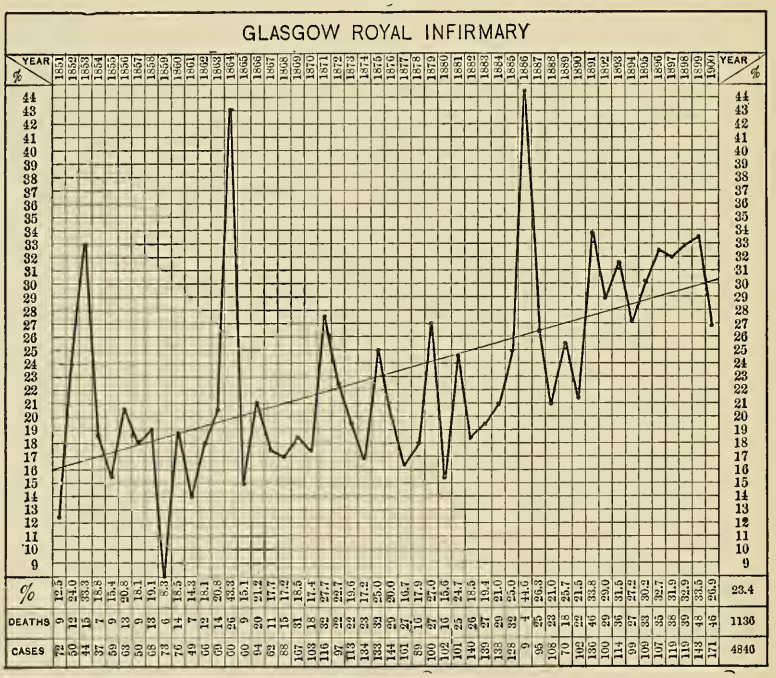
Month.	Cases.	Per Cent.
January	3,452	9.98
February	3,257	9.42
March	4,256	12.31
April	4,513	13.05
May	4,287	12.39
June	2,546	7.36
July	1,845	5.33
August	1,457	4.21
September	1,548	4.48
October	1,981	5.73
November	2,548	7.37
December	2,897	8.38

The records collected by Wells of 685,566 fatal cases show:

Month.	Cases.	Per Cent.
January	83,151	12.1
February	86,090	12.5
March	89,062	13.0
April	89,263	13.0
May	67,028	9.9
June	38,861	5.7
July	26,059	3.8
August	24,811	3.6
September	27,183	4.0
October	38,111	5.7
November	50,260	7.3
December	65,667	9.6

These tables show a fact long well recognized, namely, that the majority of cases occur between November and June. A study of this subject has been made by Newsholme based on the statistics of different cities in various parts of the world, with practically the same conclusions. Hardie, who has

FIG. 63.



investigated the problem in Australia, found that the greatest number of deaths from pneumonia occurred in August and September, which he attributes to the exhausting heat, and to the fact that when the air is dry it is a better carrier of microörganisms.

(*c*) *Geographical Distribution.*—Pneumonia is ubiquitous, but is less prevalent near the equator and near the poles than in the intervening zones. In hot climates it is most often encountered in elevated sections, in which

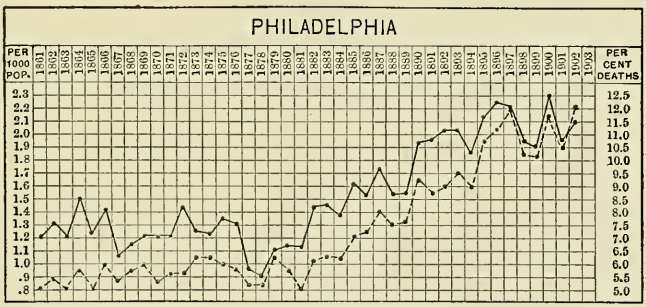
sudden changes of temperature are frequent and marked, the broiling midday sun being rapidly replaced by cold nights.

The United States census of 1900 shows that the proportion of deaths due to pneumonia was greatest in the South Mississippi River belt (142), where there is a large negro population; in the middle Atlantic Coast region, (134.6); and the Cordilleran—western states somewhat removed from the coast—region (118.7). It was least along the Pacific coast (78.6), the heavily timbered region of the Northwest (79.4), and along the coast of the Mexican Gulf (80.3).

(*d*) *Meteorological Influences.*—While there seems but little doubt that these have a distinct although indirect influence on the occurrence of pneumonia, and although a good deal of investigation has gone on in the endeavor to throw light on the subject, yet, owing to the complexity of the problem, an exact scientific solution of it is still unattained.

Most writers have attributed a predisposing potency to change of temperature, particularly if this be rapid and marked in degree, a contention which is borne out by many statistics. On the other hand, as Fraenkel has pointed out, in certain localities such as London, Dublin, Wurzburg and Tübingen, most of the pneumonia cases occur during those winter months in which, while the actual temperature is lower, yet the daily variation is less than during the spring. Keller states that the frequency of pneumonia varies inversely as the amount of rainfall. According to Purjesz, this statement has been cor-

Fig. 64.



roborated by a number of different observers as holding good for Kiel, Denmark, Vienna and Munich. Certainly this contention would seem reasonable enough from the fact that bacteria do not rise from a moist surface.

Regarding the effect of atmospheric pressure, humidity and high winds, our knowledge is less definite. The last assists the dissemination of the infective agent, makes the cold more penetrating, and also affects directly the barometric pressure and the temperature. "Latitude seems to have but little influence upon the death-rate, since New York State, which gave the largest mortality (228.4 per 100,000 population), and Michigan, which gave the smallest (109.3) in 1900, are almost parallel as regards the location of their cities.[1]

The relation of pneumonia to the average absolute humidity by months for a period of ten years, 1877 to 1886, in Michigan (H. B. Baker), is shown in the table following:

[1] Sajous, *Monthly Cyclopedia of Practical Medicine,* vol. xviii.

	Jan.	Feb.	March	April	May	June	July	August	Sept.	Oct.	Nov.	Dec.	Annual Average.
Pneumonia . . .	57.9	63.1	61.1	53.9	39.3	25.1	16.1	13.3	16.7	21.3	33.4	44.8	36.5
Average absolute humidity	1.38	1.51	1.81	2.75	3.91	5.27	6.07	5.84	4.98	3.71	2.3	1.73	3.44

It has been taught ever since the days of Hippocrates that dampness and cold were factors which favored the development of pulmonary diseases. The foregoing table shows that certainly so far as dampness is concerned this is not true. It will be seen that in the months with the greatest amount of humidity the fewest cases of pneumonia occurred.

The relation between pneumonia and the average temperature of the atmosphere in Michigan, by months, 1877 to 1884, (H. B. Baker), is as follows:

	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Pneumonia[1]	62.	66.	62.	56.	42.	27.	18.	14.	18.	23.	35.	48.
Atmospheric temperature F.....	21.43	25.60	31.04	44.48	56.60	65.54	70.68	68.85	62.05	51.34	35.99	27.25

From the foregoing data it is evident that statistics can be adduced both to prove and disprove the etiological factor of cold. Lavoisier and Seguin long ago demonstrated that warm-blooded animals, including man, absorbed more oxygen and eliminated more carbon dioxide when exposed to cold, which would indicate that "more heat energy is liberated, and that the efficiency of the bacterial and antitoxic properties of the body fluids, including those of the respiratory tract, is increased in proportion" (Sajous). There is not much doubt, however, that although a moderate amount and degree of cold may stimulate, too prolonged or severe exposure may depress. Furthermore, it is not only a question of cold but also of humidity and other meteorological influences. Again, Loewy has shown that this reaction on the part of the human economy to cold is for some reason lacking in certain individuals, in those, for instance, in whom shivering does not take place.

It must also be remembered that although cold and dampness may be predisposing factors, it is at the times when these conditions exist that people are most apt to live in crowded quarters, with insufficient ventilation, and that hence the chances of direct infection are much increased, to say nothing of the fact that at such times the temptation to indulge in alcoholic stimulants is greater.

Anders[2] has written a very comprehensive article upon the subject of meteorological influences. His conclusions are as follows:

1. That the seasons exert a marked effect upon the prevalence of lobar pneumonia, the maximal mortality being observed during the winter and spring months.

[1]Indicating what percentage of all reports received stated the presence of pneumonia then under the observation of the physicians reporting.

[2]*American Medicine*, vol. viii, September 3, 1904, p. 407

2. That insular climates probably manifest the greatest rise in pneumonia mortality in winter, while that of continental climates coincides mainly with spring.

3. That the mortality of the epidemic form of the disease is, to a less extent, influenced by the seasons and that it may occur in the fourth and even third quarter of the year.

4. That an apparently close relationship exists between periods of low temperature and the death-rate from pneumonia.

5. That the mortality rises and falls with the barometric pressure, the maximal level being reached during periods of highest pressure and *vice versa*; that the barometric pressure, however, is governed by the temperature, being inversely as the latter, is to be recollected.

6. That the average velocity of the winds and the death-rate from this disease would appear to stand to one another in relation of cause and effect (a provisional explanation of this fact being found in the controlling influence exerted by the winds upon temperature and barometric pressure).

7. That the coincidence of existing low temperatures, high barometric pressure, the direction and velocity of the winds and maximum mortality from pneumonia, is so uniformly constant as to merit serious consideration, and suggest a close and direct relation between their combined influence and the progress of mortality from pneumonia.

8. That the mean relative humidity of the atmosphere shows equally decided variability during the periods of abeyance in the prevalence and fatality of the disease with that of the cold or annual pneumonic season.

9. That the major influence exerted by the seasons, however, is probably not direct (*e. g.*, by a lowering of the bodily resistance due to low temperature, high barometric pressure, direction and velocity of the winds, etc.), but indirect, namely, by bringing about that effective element in the causation, concentration and increased virulence of the specific poison in consequence of closed doors and windows and lack of free ventilation.

(*e*) *Epidemics.*—Accounts of supposed pneumonia epidemics go back nearly as far as written history itself. An exhaustive tabulation has been made by Wells,[1] who gives a list of epidemics extending back to 1440. It has been supposed by some that the plague of Athens, which destroyed one-fourth of the population, having previously devastated the shores of the Mediterranean, as well as the Black Death, which ravaged Europe during the middle of the fourteenth century, were forms of pneumonic infection. The truth of these beliefs will perhaps never be established, but it is unquestionable that pneumonia epidemics have occurred and continue to do so from time to time, not infrequently in company with some other disease such as influenza. This is shown by Poehlmann's figures: at Erlangen, in 1886, pneumonia represented 4 per cent. of all morbidity; in 1887, 10.58 per cent.; in 1888, 11.39 per cent.; and in 1885, only 3.3 per cent. The most reasonable explanation of these epidemics is an increased virulence on the part of the infective agent. Many of them are stamped with a distinct individuality of their own; for instance, in some diarrhœa may be a very prominent feature, or insomnia, intense prostration, jaundice, cerebral symptoms, dyspnœa, etc.

In the Alaska epidemic of 1881, with one exception, only natives were attacked. At Obersichte the disease was limited to children under five

[1] *Journal of the American Medical Association*, February 23, 1889; and *Medical News*, May 20, 1905.

years of age; at Kimberly to the Kaffirs. In an epidemic in Boston in 1876, the onset was very insidious, the course prolonged, and hemorrhages common. In Ireland in 1854 and in Italy in 1898, the attacks were extremely mild in character. "In the epidemic of Deri Gazi Kahn, in which 40 out of 550 persons lost their lives in a few weeks, the local morbid process proceeded with the utmost rapidity through all the stages of inflammation to suppuration, abscess and gangrene. Both lungs were usually affected, and after death were found to be, to a great extent, disorganized" (Wells).

A study of Wells' tabulation shows that the spring and winter months have contributed the greatest number of epidemics and further, they have appeared in all parts of the world, although most frequent in the elevated regions of northern Italy, southern France, and Switzerland.

Edsall and Ghriskey have reported a small hospital epidemic as follows: A patient died of pneumonia in bed 3 of a side ward in the Episcopal Hospital at Philadelphia. Within the next eleven days two patients placed temporarily in this bed developed pneumonia, pneumococci being found in the blood. On the twelfth day a patient in a neighboring bed was found to have pneumococci in his blood, but no symptoms developed.

Tyson quotes an instance in which "out of a ship's crew of 815, 410 were attacked in rapid succession, and out of 720 attacked, 298 fell victims." Jürgensen states that pneumonia is a house disease. "In the village of Lustnau, there were 223 dwellings in which during a period of eight years the disease occurred once in 40 houses, several times in 44, and not at all in 139." Poor drainage and inadequately drained land have been held to favor the development of pneumonia. There can be no doubt, however, that overcrowding and bad ventilation are potent factors. In the jail at Moringen in 1878 there were from 700 to 900 inmates, of whom 58 developed pneumonia. Kerschensteiner reported 161 cases with 46 deaths, among 1,150 inmates of the prison at Amberg in 1880. Similar epidemics have been reported in French and German army barracks, and in the English navy. Schroeder showed that one house at Kiel furnished the local clinic with 34 cases of pneumonia during a period of fourteen years. Jaworski and Chrostowski treated 5 cases of pneumonia in one house which had not been free from disease for twenty-eight years. Emmerich and Netter have demonstrated the presence of the pneumococcus in the dust of rooms occupied by pneumonia patients: probably droplet infection during coughing and speaking does much to disseminate the contagion.

Ballard has "reported 490 deaths due to pneumonia, caused in the most part by eating infected bacon. According to this observer, those who had the disease could transmit it to others who had not eaten of the meat, a fact which has been noticed in many other instances. After having been kept for several months the bacon lost its toxicity. This epidemic was known as the Middlesborough pneumonia epidemic." Numerous cases are on record in which nurses have been taken down with pneumonia promptly after or even while taking care of patients ill with this disease, and in which different members of the same family, or fellow lodgers in boarding-houses have been attacked within a short space of time. Thus, in one instance the disease began in a boy. After he had been ill three days two other children were attacked One day later the mother succumbed, and on the same day the father, returning from a journey, was also seized, his attack terminating fatally. In each instance the onset had been sudden, the temperature high

and the prostration severe. Investigation revealed the fact that there was a direct communication between the dining-room of the house and the main drain (Copman). Tarchetti and Curlo relate another instance in which an entire family succumbed to the disease in a short time, an event which they attribute to two factors, increased susceptibility to pneumococcic infection and increased virulence of the diplococcus as it passes from one human organism to another. In this instance the weakest and least healthy individual was first attacked, and the most robust, last. Infection derived from handling of the bedclothes is exemplified by the following case reported by Kühn: A man was attacked by pneumonia and soon afterward several of his servants who had been cleaning his clothes became ill. One maid who had been thus exposed returned to her home, situated some distance away, carrying with her some linen which had been used in the sick-room. Eight days afterward both she and her sister who occupied the same bed developed pneumonia. Mendelssohn has reported instances in which patients were attacked by pneumonia soon after being placed in beds previously occupied by individuals ill with this disease. Such cases are of no great rarity.

An epidemic of pneumonia in an isolated village of 454 inhabitants, in which 14 per cent. of the population developed pneumonia within a period of two months, has been recorded by Spaet. Similar examples could be quoted almost indefinitely, but the explanation of these facts must come from a more thorough knowledge of bacteriology. Upon such a knowledge is based the main hope for the future. The fact that improved hygienic measures have thus far failed to check the prevalence of pneumonia, and that the application of antiseptic measures has been equally unavailing indicates the limitations of our information upon the question of transmission.

Infection from Animals.—Pleuropneumonia contagiosa is a disease well known to veterinarians. The disease occurs in barracks and livery stables, attacks chiefly the larger horses, and is transmissable from one to another either directly or by means of an intermediate host. Fraenkel relates an instance, in the spring of 1884, in which such an epidemic existed among the horses of the Westphalian Artillery at Minden. Soon afterward an epidemic of pneumonia broke out among the soldiers which was limited almost exclusively to those individuals who came in intimate contact with the horses. Numerous similar epidemics occurring in the German army are on record. In one of them a microörganism was isolated from the bronchial secretions of the horse which was indistinguishable from the pneumococcus. According to the Paris correspondent of the *British Medical Journal*, 70 cases of psittacosis (pneumonia transmitted by parrots) have occurred in that city since 1892.

To sum up, we are forced to the conclusion that pneumonia is a transmissible disease, to be classified with the infectious fevers, and like them to be guarded against by the application of antiseptic principles; for although the virulence of its infectiousness is as a rule not very great, it is under certain circumstances undoubtedly capable of transmission from person to person.

II. Individual Factors.—(*a*) *Cold.*—It is generally believed that hunger, fatigue, and exposure to cold are predisposing factors; but that something over and above these is required is shown by the fact that very little pneumonia existed in Napoleon's army during the retreat from Moscow. Again pneumonia is very frequent in very early and in very advanced life, times at which the "cold" factor does not play an important role. The effect of cold

upon the organism has been explained as causing a retention of waste products of metabolic activity, variation in blood pressure, impairment of cellular metabolism, and reflex action. Corroborative evidence as to cold being an etiological factor has been furnished by the experiments of Lode, who exposed animals one-half and two-thirds shaved, to heat, then cold, whereupon they were inoculated with pneumobacilli. Of the animals thus treated 85 per cent. died of pneumonia and pleuritis, while only 12 per cent. of the unshaved and unexposed ones did so. Similar results were obtained by Lipari, who made intratracheal injections of pneumonic sputum in animals, and found that a much larger proportion developed pneumonia if they had been exposed to cold than was otherwise the case. Among 4,244 cases collected by the writers, 755 (17.79 per cent.) gave a history of exposure and "catching cold."

(*b*) *Trauma.*—Although the existence of "konkussions-pneumonie," as described by Litten, has been questioned by a number of authorities, there seems little doubt that trauma may and does in a certain proportion of cases have a distinct etiological influence. Souques[1] has reported 49 cases of typical croupous pneumonia following contusions of the thorax without actual injury to the lung tissue. These cases usually occur after direct blows upon the chest, or injuries produced by falling weights, or crushing force. Pneumococci have been found in the lungs in a number of cases, although in the majority the burden of proof was placed upon the occurrence of these organisms in the expectoration. It has been stated that cases of traumatic pneumonia show an increased amount of blood in the sputum.

Among 6,790 cases collected by the writers, 58 (0.85 per cent.) gave a history of injury. Ashton and Landis found 7 cases in 991 in which trauma was probably an etiological factor; Moelmann one in 944. Baeck, who found 5 such cases among 340, noted a very high leukocytosis, the percentage of fatalities being, however, much the same as in other cases.

(*c*) *Immersion in Water.*—Fraenkel has seen about one dozen cases apparently due to this cause. Bein has reported similar ones. Many of these terminate favorably. Norris reported a case of a stoker who jumped overboard into the Delaware river in mid-winter; he was brought into the Pennsylvania Hospital with a temperature of 94° F. and physical signs of pneumonia; recovery followed. Among 830 cases collected by the writers, 66 had received a wetting (7.9 per cent.).

(*d*) *Aspiration Pneumonia.*—Stubenrath,[2] from experiments with animals, concludes that this form of pneumonia is dependent upon mechanical influences of aspiration without regard to the fluid used.

(*e*) *Inhalation Pneumonia.*—Pneumonia has been reported as the result of inhaling irritating substances such as dust, ether, and nitric acid fumes. Most of these were of the lobular type. Merkel gives the following morbidity figures for certain occupations: painters, 7.5 per cent.; room cleaners, 6.9 per cent.; porcelain makers, 5 per cent.; cement makers, 4 per cent.

(*f*) *Occupation.*—This plays an etiological role. Gründler states that the recruits at Magdeburg are very predisposed to pneumonia until they become accustomed to their work, as shown:

[1] *Presse Medicale*, vol. vii, p. 109, 1900.
[2] *Ueber Aspirations Pneumonie*, etc., Würtzburg, 1898.

	Men.	Cases.	Per Cent.
Recruits (1st year)	2,226	48	2.15
Soldiers (2nd year)	2,076	17	0.81
Soldiers (3rd year)	1,031	7	0.67
Soldiers (beyond 3rd year)	675	1	0.14

Emigrants are more susceptible than natives who have become acclimated. The United States census report shows that whites of foreign birth are much more frequently attacked than the native born. Outdoor occupations show a higher morbidity from this disease than indoor vocations.

Different races of men have in the course of centuries developed well-marked and distinct characteristics, which have fitted them to live in given localities. This is exemplified physically by varying degrees of pigmentation, psychically by varying types and degrees of mental activity, and economically by differing diet and mode of life. When a man emigrates to other degrees of latitude than those for which his heredity fits him he falls an easier prey to disease than the native. This is well exemplified in the case of the Lapps, who whenever they move from the frozen north to a temperate zone almost invariably die of pneumonia within a short time.

Sanitation is also of importance and closely allied with the question of cleanliness is that of ventilation. Pneumonia is distinctly more prevalent in cities than in the country, despite the fact the outdoor work preponderates in the latter, indicating that poor hygiene and overcrowding, with the attendant danger of infection, are more important factors than climate and temperature. Anders, who investigated the question in Philadelphia, found the highest mortality from pneumonia in the most densely populated wards, and in those occupied by negroes and foreigners.

The influence of occupation upon the frequency of pneumonia is shown by the mortality statistics of the United States census, 1900.

PERCENTAGE OF ALL DEATHS DUE TO PNEUMONIA.

Males.	Whites.	Negroes.
Professional	8.7	11.8
Clerical and official	9.2	6.6
Mercantile and trading	9.4	13.5
Public entertainment	9.9	18.7
Personal service, police and military	9.9	11.9
Laboring and servant	11.8	11.7
Manufacturing and mechanical industries	9.8	10.2
Agricultural, transportation, and other outdoor	10.7	13.8
All others	8.3	12.5

This indicates that the death-rate is considerably higher in the negro than in the white man; and higher for indoor than for outdoor occupations.

PERCENTAGE OF ALL DEATHS DUE TO PNEUMONIA.

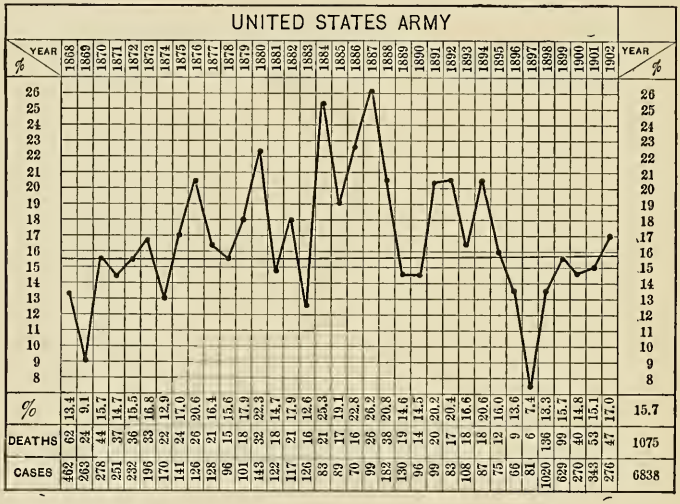
Females	Whites.	Negroes.
Musicians and music teachers	5.2	——
School teachers	7.4	8.8
Stenographers and typewriters	6.0	——
Bookkeepers, clerks, copyists	13.0	——
Hotel and boarding-house keepers	5.0	4
Laundresses	10.3	8.1
Nurses and midwives	10.1	9.4

(Continued on next page.)

Males.	Whites.	Negroes.
Servants	9.5	8.3
Cigar makers and tobacco workers	12.2	——
Mill and factory operatives—Textiles	9.8	6.0
Milliners	5.6	5.2
Dressmakers and seamstresses	8.0	7.2
Telegraph operators	8.6	——
All others	9.5	8.8

Pneumonia in the National Armies.—The following diagram, after Wells, shows the prevalence of pneumonia in the United States army from 1868 to 1902. The total of 6,838 cases with a general mortality of 10.75 per cent. is in startling variance with that of the German army, in which among 40,000 cases the death-rate was only from 3 to 4 per cent., and suggests that as there

Fig. 65.



is no parallel diversity in the methods of treatment, we have to deal in this country either with an infective agent of much greater virulence, or an individual with lower resistance.

The following data show the frequency and mortality from pneumonia in the different national armies (Sforza). It will be noticed that incidence and mortality tend rather to vary inversely than directly:

	Morbidity. Per Cent.	Mortality. Per Cent.
United States Army	2.9	14.7
English Army	4.5	12.2
Italian Army	5.0	9.5
Austrian Army	6.0	8.3
French Army	6.6	9.2
Russian Army	8.0	8.0
Prussian Army	9.4	3.5

(*g*) *Alcoholism.*—Alcoholic intoxication seems to be a predisposing cause. Of 2,407 cases collected by the writers, 130 were intoxicated at the time the pneumonia appeared. Moelmann found 26 in 380 (6.8 per cent.). Doubt-

less the exposure incurred at such times contributes to the development of the disease.

(*h*) *Previous Attacks.*—Among the writers' cases collected in reference to this subject, 1,615 out of 11,811 had previous attacks (13.6 per cent.), and of 246, 189 were in the second, 33 in the third, 18 in the fourth, 3 in the fifth, 1 in the sixth, 1 in the eighth, and 1 in the ninth attacks. Among 2,137 there were 41 (1.9 per cent.) who had previous attacks of pleuritis; 112 (6.7 per cent.) among 1,675 had bronchitis before pneumonia, and 94 (24.8 per cent.) among 379 who had previous attacks died.

	Males.	Females.
Previous attacks within 1 year	11	1
Previous attacks 1 to 5 years	17	4
Previous attacks 5 to 10 years	10	4
Previous attacks 10 to 20 years	8	1
Mortality	29 per cent.	10 per cent.

Proximity of Recurrence.—Norris found 56 cases in 500 who had more than one attack. In 944 cases, Moelmann found 54 patients who had had more than one attack. Fifty-six per cent. of these were grave, 20 per cent. light, and 24 per cent. abortive; of these 7 died. He is certain that an individual predisposition exists, which increases from year to year. He also holds that there is often a family disposition, when the parents had tuberculosis, pneumonia, chronic pulmonary disease, or have been alcoholics. Instances of an individual being attacked by pneumonia four times have been recorded by Landsberg, and Lepine and Froment. Chomel saw pneumonia in the same individual ten times, Frank eleven times, and Rust recorded an instance of a person being attacked twenty-eight times. Preble saw a child of eight years in the fifth attack. Bokai saw three attacks of pneumonia in a boy within forty-eight days, involving in each instance the same lobe. Statistical data similar to the foregoing could be quoted almost indefinitely. There seems to be no doubt that recovery from each attack of pneumonia makes a subsequent one still more likely. In a certain number of cases, however, successive attacks seem to be milder in character.

(*i*) *Acute Illnesses: Influenza.*—Pneumonia is well known as one of the most fatal complications of influenza. Epidemics of these two diseases often occur together. In a certain number of cases when they occur coincidently, the pneumonia is of the lobar variety, and is in no way distinguishable, macroscopically or microscopically, from typical croupous pneumonia (Fraenkel).

Typhoid Fever.—There is much confusion in regard to the relationship between typhoid fever and pneumonia. Undoubtedly many cases clinically classed as "typhoid pneumonia" are really forms of tuberculous disease. Others again are due to the typhoid bacillus. Among 4,459 cases of pneumonia collected by the writers, typhoid fever was coincidently present in 64 (1.4 per cent.). Typhoid fever may predispose to pneumonia by lowering the general bodily resistance.

Pulmonary Tuberculosis.—Does pneumonia favor the development of tuberculosis? Is tuberculosis greatly aggravated by pneumonia? Do the two conditions frequently co-exist? There is probably frequent confusion between the two diseases. On the one hand, apical disease of pneumococcic

origin, if there be delayed resolution, may closely simulate tuberculosis. On the other hand, tuberculous pneumonia, in which the pneumococcus plays no part, is of frequent occurrence and may, under certain conditions, resolve to a remarkable degree, for a time, at least, and, if "consumption" subsequently develops, gives rise to the belief that a pneumonia was the cause of a *locus minoris resistentiæ*. It is well, therefore, to "be suspicious of an atypical pneumonia."

Louis stated that a pneumonia engrafted on a tuberculous lung may "terminate rapidly and favorably." Walshe says, "If the lungs already tuberculized become actually inflamed, convalescence from the pneumonia often takes place as rapidly as if the lungs had previously been sound. . . . . Some of the most marked examples of rapid resolution I have met with were in phthisical persons." Grisolle, Bergtold and many others hold similar views. Huss described 36 such cases with a mortality of 33 per cent. In some cases the pneumonia does not seem to have much effect on the tuberculous process, but it frequently happens that a rapid disintegration of pulmonary tissue, or a generalized miliary tuberculosis promptly follows.

R. W. Phillip concluded from the study of 1,000 cases of tuberculosis that there was a traceable close sequence of tuberculosis upon pneumonia in only 0.5 per cent. Among 2,924 cases of tuberculosis treated at the Phipps Institute in Philadelphia, during the first two years, 510 gave a history of having had pneumonia (17 per cent.). As the previous occurrence of pneumonia is one of the questions which is routinely tabulated in every case, these figures speak more authoritatively than those gathered from general histories by Wilson Fox, Grisolle, Louis and others, who found a much smaller proportion, although it is of course possible that some of these supposed pneumonias were not pneumococcic in origin.

Regarding the increased activity of a tuberculous process which occurs at times after an attack of pneumonia, Cornet suggests that "the exudation of the latter disease may, as it were, wash out and destroy the areas of peripheral resistance of those tubercles which lie within its focus." In 127 pneumonia autopsies collected at the Pennsylvania Hospital, Philadelphia, Norris found 11 instances of gross tuberculous lesions. The lungs were involved in 8, the peritoneum in 1, the bronchial lymph nodes in 2. Croupous pneumonia and tuberculosis have been encountered elsewhere as follows: Vienna, 1.1 per cent.; Stockholm, 1.4 per cent.; Basel, 1.8 per cent.; Rychner, 2.7 per cent.; Norris, 1.4 per cent.; Musser, 0.8 per cent.; Biach, 1.7 per cent.; Sello, 2.0 per cent.; A. H. Smith, 0.8 per cent.; J. McCrae, Fyshe and Ainley, 1.6 per cent.

(*j*) *Chronic Diseases.—Diabetes.*—There is a marked discrepancy among the figures of different observers as to the frequency with which pneumonia occurs in patients with diabetes mellitus. There seems to be no doubt, however as to the higher mortality of pneumonia when complicated by diabetes. Diabetes mellitus occurred in 2 out of our 2,949 collected cases. Severe complications such as pulmonary gangrene not infrequently occur when pneumonia attacks diabetic subjects.

In other chronic diseases, such as *nephritis, arteriosclerosis, hepatic cirrhosis,* and the like, pneumonia often supervenes as a terminal infection, and the same may be said of diabetes mellitus. Anders, who has investigated the frequency of *cardiovascular lesions* in pneumonia at the Philadelphia General Hospital, found that, in 275 autopsies on individuals dead of this

disease, such lesions existed in 250, or 90.9 per cent., most of which were chronic endocarditis and endarteritis; whereas these lesions were found at autopsy, death being due to different causes, 380 times in 1,600 cases (25 per cent.) at the Charing Cross Hospital in London, and 83 times in 142 at Toronto, including patients of all ages (58.5 per cent.). In 127 autopsies, Norris found high grade arteriosclerosis 14 times (11 per cent.). It is a very common thing for hemiplegic patients to die of pneumonia, and not infrequently the lung on the paralyzed side is attacked.

(*k*) *Age.*—This plays a well-defined role both in the frequency and mortality. The following table collected by the writers, based upon 32,681 cases, shows that by far the greater number of cases occur in early adult life. The United States census report which follows places the majority at the extremes—a discrepancy which is to be explained by the fact that the latter statistics are based upon fatal cases. Among 32,681 cases:

Age.	Cases.	Per Cent.
0 to 5 years	1,249	3.8
5 to 10 years	3,132	9.6
10 to 20 years	5,107	15.6
20 to 30 years	8,041	24.6
30 to 40 years	5,665	17.3
40 to 50 years	3,987	12.2
50 to 60 years	2,558	7.8
60 to 70 years	1,754	5.4
Over 70	1,094	3.3
The age was not stated	94	0.3

United States Census Report, Per 1,000 Cases of Pneumonia

Census Year.	1–5 yrs.	5–19 yrs.	20–39 yrs.	40–59 yrs.	60+
1890	304.7	70.2	195.8	203.9	225.4
1900	382.6	59.1	147.6	171.5	239.2

(*l*) *Sex.*—Of 12,098 cases collected by the writers, 8,881, or 73.41 per cent., occurred in males and 3,217, or 26.59 per cent., in females. The various relations of incidence to sex and age are shown in the following tables:

Age.	Males.		Females.	
	Cases.	Per Cent.	Cases.	Per Cent.
0 to 5 years	35	0.39	22	0.68
5 to 10 years	57	0.64	37	1.15
10 to 20 years	2,197	24.74	456	14.18
20 to 30 years	2,912	32.79	853	26.51
30 to 40 years	1,582	17.81	542	16.85
40 to 50 years	1,117	12.58	425	13.21
50 to 60 years	593	6.68	403	12.53
60 to 70 years	310	3.49	319	9.92
Over 70	78	0.88	160	4.97
	8,881		3,217	

In adult life the incidence is usually estimated as 6 to 4, for male and female respectively. In early life this difference does not seem to exist, which would indicate that the greater exposure entailed by male occupations is the main factor in the causation of the difference. Out of a total of 35,798 cases collected by the writers, 19,848, or 30 per cent., were females, 24,950,

or 69.7 per cent., were males. The census of 1900 shows that in the United States 58,340 men, and 47,631 women died of pneumonia.

(*m*) *Race.*—The negro race appears to be more susceptible to pneumonia than the white. This may be explained in part by color and conformation. In the negro the skin is functionally more active in the throwing off waste products and owing to the color, heat radiation is greater; it is very evident that the same degrees of cold would cause more marked systemic and metabolic effects than in the white. In the United States census report of 1880 the relative frequency of pneumonia in the negroes was one-half more than in the whites. In the British army, pneumonia was more prevalent in the blacks in the proportion of 33 to 20.2. Furthermore, poor hygiene, as well as alcoholism, are very common among our negroes. The American Indian and the Esquimaux also seem to be very susceptible, whereas the Malays, and the natives of Hindoostan and Burmah, as well as the Chinese, have much more resistance. Again there is considerable difference in different branches of the same race, thus, the Celt is more susceptible than the Teuton.

(*n*) *Insanity.*—Pneumonia, according to Krafft-Ebing, is the cause of death in one-sixth of all cases of insanity. This statement, however, includes the hypostatic types so often seen in marantic dements, and in the pneumonia of vasoparesis met with in paralytics (Gaye). In the insane, pneumonia is very apt to have an insidious onset, and to run a symptomless course, save for such manifestations as anorexia and weakness.

Bacteriology of Pneumonia and the Pneumococcus Infections.—The study of the infectious nature of pneumonia dates from the observations of v. Jürgensen, in 1874. Long before routine bacteriological investigations were begun, he placed pneumonia among the infectious diseases and assumed it to be due to a specific cause. He also regarded it as a general disease with local manifestations in the lung. A year later Klebs described micrococci which he had found in a pneumonic exudate and to which he gave the name of "*Monas pulmonalis.*" Eberth, in 1880, reported the appearance of diplococci in sections of a solidified lung and in the purulent meningeal exudate of the same case. A similar organism was pictured by Koch in the following year. The organism described by each of these investigators was in all probability that now known as the *Micrococcus lanceolatus*, but these observations, on account of the imperfect bacteriological methods of that time, have only historical interest. In 1883, Friedländer announced the discovery, in pneumococcic exudates, of an organism termed by him the pneumococcus, which was capable of causing pleuropneumonia in mice and occasionally in guinea-pigs. Later investigations however demonstrated this organism to be an encapsulated bacillus, now generally known as Friedländer's pneumobacillus, and but infrequently associated with lobar pneumonia.

The microörganism which has been shown to be constantly associated with acute fibrinous pneumonia was first thoroughly studied by Sternberg, in 1880, though its relation to pneumonia was not appreciated by him at that time. He found that his own saliva, when injected into rabbits, caused the death of these animals, and that from their bodies an organism could be recovered which was peculiarly pathogenic to them. To this organism he gave the name of *Micrococcus Pasteuri.* At about the same time Pasteur found an identical diplococcus in the saliva of a child suffering from hydrophobia. Although Sternberg's observation antedated that of Pasteur the

discovery is credited to the latter by priority of publication. A little later, interesting observations were made by Talamon but it was not, however, until 1884, as the result of the labors of A. Fraenkel, that this organism was shown to have a definite and constant relation to pneumonia. Fraenkel isolated it from the sputum of individuals suffering from pneumonia, demonstrated its constant presence in the solidified lung, and, with pure cultures, produced exudative lesions of the lungs of mice and guinea-pigs and general septicæmia in rabbits. He stated definitely that it was in all probability the causal agent of pneumonia.

The routine examinations of Weichselbaum (1886), Netter (1890) and others have demonstrated this organism to be so constantly present in the exudate of genuine acute lobar pneumonia that it may be considered as the chief etiological agent. Other organisms are occasionally associated with it, and are found rarely in the absence of the pneumococcus in an apparently typical lobar pneumonia; but in the great majority of reported cases the *Diplococcus lanceolatus* is present and in pure culture. Weichselbaum's study included a group of 129 cases of lobar and lobular pneumonia and in 94, 78 of which were of the lobar type, Fraenkel's diplococcus was found. Netter states that it occurred in 75 per cent. of his cases. Wolff found it in 66 of 70 cases and Pearce in 110 of 121. The studies of Gameléia, Welch, Wright and Stokes, Howard and others, based on smaller groups of cases, give similar results. Gamaléia considers the Friedländer bacillus to be only occasionally accidentally present; on the other hand neither Pearce nor Howard found it in pure culture in primary croupous pneumonia. It may, however, be found in bronchopneumonia and in irregular forms of diffuse pneumonia characterized by a viscid exudate poor in fibrin. The term *pneumococcus*, first applied by Friedländer to his bacillus, is now the common name for Fraenkel's diplococcus; while *pneumobacillus* is frequently used to indicate the former.

Although the pneumococcus is found in pure culture in the majority of cases, secondary invasion by other organisms is not uncommon. The *Streptococcus pyogenes* is the more common associate of the pneumococcus and less frequently the *Staphylococcus pyogenes aureus*, the *Bacillus diphtheriæ*, the *Bacillus influenzæ*, *Bacillus typhosus*, and bacilli of the group of *B. capsulatus mucosus*.

The Pneumococcus.—**Nomenclature.**—The microörganism of lobar pneumonia has received a variety of names. Without going into the question of proper nomenclature these various names may be reviewed; *Microbe de la salive* (Pasteur), *Coccus lancéolé* (Talamon), *Micrococcus Pasteuri* (Sternberg), *Pneumococcus* (Fraenkel), *Diplococcus pneumoniæ* (Weichselbaum), *Bacillus salvarius septicus* (Flügge), *Klebsiella salvarius* (Trevisian), *Streptococcus lanceolatus* (Gamaléia), and *Micrococcus pneumoniæ cruposæ* (Sternberg). At present the terms *pneumococcus*, *Diplococcus pneumoniæ*, and *Micrococcus lanceolatus* are in common use. Chester in his recent classification uses the term *Streptococcus pneumoniæ*.

Morphology and Cultural Characteristics.—The organism is seen as elliptical or lance-shaped cocci occurring in pairs or chains of four to six elements. In sputum or fresh exudates a distinct capsule is seen about the organism; this is not evident in cultures on ordinary media. It stains readily with the usual dyes and also by Gram's method. The organism can be cultivated readily on all culture media except potato, and grows more

luxuriantly on slightly alkaline media. On the surface of gelatine at a temperature of 24° C. the colonies appear as small round circumscribed finely granular white or grayish points, which never liquefy the gelatine. On agar slants, at the temperature of the body, the colonies are transparent and delicate and scarcely visible to the naked eye. Growth in milk is characterized by acid production and coagulation of casein. In Hiss' inulin-serum-water medium the pneumococcus causes coagulation and this medium is therefore of importance in differentiating the pneumococcus from the *Streptococcus pyogenes*, which under some circumstances may closely resemble it morphologically.

The recent studies carried out under the direction of the Commission for the Investigation of Acute Respiratory Diseases of the Department of Health of the City of New York, included a comparative study of the pneumococcus and pneumococcus-like organisms. Park and Williams found that the so-called *Streptococcus mucosus* of Schottmüller, which has hitherto been classed with the true streptococci, possesses characteristics which demand that it be classed as a definite variety of pneumococcus and recommend that the name be changed to *Streptococcus lanceolatus, var. mucosus*. Collins' agglutination tests show this organism to be more closely related to the *pneumococcus* than to the *Streptococcus pyogenes*, thus supporting the conclusion of Park and Williams. Hiss' observations as well as those of Duval and Lewis also support this view.

The Pneumococcus in Apparently Healthy Individuals.—Since Sternberg demonstrated the presence of the pneumococcus in his own saliva many observations have been made concerning its frequency in the buccal secretions from normal individuals. Netter found it in 20 per cent. of the persons whom he examined and investigators of the New York Commission report its presence in from 46 to 85 per cent. The question of town or country habitation or of indoor or outdoor occupation appears to make little difference in the frequency. A higher percentage of atypical strains was obtained from healthy persons than in those suffering from pneumonia.

Buerger's studies show that the organism is slightly more frequent in males than females and is most frequent in children. It may persist for considerable periods of time. Longcope and Fox found the percentage of the typical forms to increase rapidly in December and January and to fall off gradually in March and April. Virulent forms are naturally not so common in normal individuals, as in pneumonia or in convalescence from pneumonia.

The Pneumococcus Outside the Body.—The pneumococcus is a distinctly parasitic organism and outside the body has only been found in the dust and sweepings of rooms and other places where dried sputum may collect. Wood has made a very extensive series of experiments to determine its viability. He found that in sputum preserved in a moist state, if not exposed to direct sunlight, it may survive a considerable time, the average duration being less than two weeks. In the dried powdered sputum the organism if exposed to sunlight or diffuse daylight dies in an hour; if kept in the dark, in about four hours. Under the ordinary conditions of the sick-room, the pneumococcus becomes harmless in about an hour and a half. The danger of infection except for those in direct contact with the patient may be entirely avoided it would appear, by ample illumination and ventilation of the sick-room.

Toxic Products.—Little is known of the metabolic products of the pneumococcus. The toxic substance is an intracellular toxin; that is, it does not

appear in soluble form in fluid media in which the organism is grown, but is intimately bound to the cell body. It can, however, be extracted in various ways from large masses of microörganisms. The freeing of the toxin in the living body is supposed to be due to the disintegration of the bacterial cells. On the other hand, the possibility of the production of a soluble toxin in the living body cannot be denied, but of this there is no proof. The difficulty of readily procuring a toxin of the pneumococcus hinders the successful production of antisera for this organism. By vaccinating animals with attenuated pneumococci or injecting extracts of the organism it is possible to produce a serum which in laboratory experiments will protect susceptible animals against many times the minimum fatal dose of virulent pneumococci. This serum is neither bactericidal nor antitoxic but belongs to a third group of antisera which appear to act through the agency of phagocytic cells. Such sera have the power to produce some change in the cocci which causes them to be more readily engulfed and digested by the phagocytes. The element which brings about this change is termed an opsonin (Wright and Douglas).

The Opsonic Index.—Rosenow, who has studied the phagocytosis of pneumococci *in vitro*, found that non-virulent strains are readily taken up by human leukocytes in the presence of normal serum, the phagocytosis being roughly proportionate to the amount of serum present. Washed leukocytes do not take up the pneumococci. Virulent strains are not taken up under any conditions until attenuated by cultivation. Pneumococci isolated from the patient's blood before, during or after crisis are not taken up by the patient's serum *in vitro*, nor by normal serum. His investigations point to the fact that during and shortly after the crisis there is a slight increase in opsonic power; and that in fatal cases this may fall below normal. Pneumonic leukocytes are more phagocytic than normal ones, as well as more resistant to heat. The pneumococcidal action of pneumonic or other blood is due to the combined action of the serum and the living white corpuscles. The serum alone of normal or pneumococcic individuals has no bactericidal action on pneumococci.

Wolf, who also studied the opsonic index, found this feature decreased in the early stages of pneumonia. In favorable cases the index rose as the crisis was approached, while it remained persistently low in fatal cases. The total antipneumococcic index—as estimated from the leukocytic, and the opsonic indices—was increased early in favorable cases, and remained high until the crisis had occurred. The experimental injection of dead virulent pneumococci brought about a similar evolution in the antipneumococcic index in normal individuals; but dead avirulent pneumococci were apparently without effect upon the pneumococcic opsonins.

The Pneumococcus in Non-pulmonary Lesions.—In the complications of pneumonia such as pleuritis, pericarditis, endocarditis, meningitis and suppurations in various parts of the body, the pneumococcus is practically always present. These secondary lesions are to be explained by direct extension, passage along lymphatics, or by a general invasion of the blood stream. Other organisms than the pneumococcus may be present in such lesions and in some instances the complications may be due to an independent secondary infection. The pneumococcus, however, is responsible for most of the complications. It is capable also of producing lesions of various organs in the absence of a primary lesion in the lung. Thus, it has been found in peritonitis, tonsillitis, conjunctivitis, inflammation of the middle ear and

the accessory sinuses of the nose, pyosalpinx, arthritis, and abscesses of various parts of the body. Randolph, who examined the conjunctival sac in 48 cases of pneumonia, found practically the same bacterial flora as in health, and suggests that the organisms normally present render the soil uncongenial to other varieties.

Pneumococcus Septicæmia.—It is now customary to regard pneumonia as general pneumococcus infection with the lesion in the lung as but one of the manifestations. Such a view of the disease allows a clearer conception of the clinical symptoms and the complications. That a pneumococcæmia, analagous to the similar condition produced in rabbits experimentally, may occur quite constantly is indicated by a very extensive series of investigations of the blood during life. Prochaska, who found the pneumococcus in all of 50 cases examined, believes the invasion to be a constant condition in pneumonia, as does Rosenow, who obtained positive results in 160 of 175 cases in which the blood was taken at all stages of the disease. Rosenow's results show that the pneumococcus may be obtained from the blood before any physical signs are evident, thus indicating that the solidification in the lung may be but the secondary localization of a primary blood infection. Pearce, in a study of 118 cases of lobar pneumonia at autopsy, found the pneumococcus in the heart's blood, liver, spleen or kidney in a little less than one-half of the cases.

General pneumococcus infection without distinct localizations has been reported by Wright and Stokes, Pearce, Flexner, Hektoen and others as the result of bacteriological examination at autopsy.

THE MORBID ANATOMY OF LOBAR PNEUMONIA.

It is customary to divide pneumonic solidification of the lung into three stages: engorgement or congestion, red hepatization, and gray hepatization or purulent infiltration.

The lung in the stage of engorgement is deep-red in color, œdematous, and slightly firmer and heavier than normal. From the cut surface a blood-tinged serum exudes. Air is still present, the lung tissue crepitates, though to a less extent than normal, and excised portions float in water. Microscopically, the capillaries of the air cells are seen to be congested and in the air cells are a few leukocytes, red blood cells, desquamated epithelial cells, small strands of fibrin and a large amount of serum. This stage lasts but a few hours as a rule, but may persist longer. As patients seldom die in this stage, opportunities for its careful study are rare.

In the stage of red hepatization the portion of the lung affected is solid, airless, and of a general brownish-red color relieved only by the carbon depositions in the lymphatics or by the grayish-yellow pleural exudate almost constantly present. The lung is firmer and heavier than normal and its size is equal to that at full inspiration. Not infrequently it shows depressions corresponding to the lines of contact with the ribs. The cut surface is comparatively dry, reddish-brown in color and presents a uniform fine granular appearance due to the protrusion of fibrin plugs from the air cells. From this surface a reddish sticky fluid with fine granular plugs may be scraped. The lung is very friable and may readily be torn. A thick mucus may be present in the large bronchi and fibrinous plugs occlude the smaller.

Microscopically, the alveoli are seen to be filled with a network of fibrin in the meshes of which are red blood cells, leukocytes and a few desquamated epithelial cells. A similar exudate may be seen in the terminal bronchi. The walls of the air cells and the supporting tissue about larger vessels and bronchi are œdematous and infiltrated by leukocytes. By proper stains diplococci may be demonstrated in the midst of the exudate. The fibrin at times may be granular or compressed and have a hyaline appearance. It is more abundant at the periphery of the alveolus and not infrequently a mass of fibrin may be seen to extend from one alveolus into another; normal openings allowing such passage have been demonstrated by Hansemann. The bloodvessels, though compressed, are usually pervious; thrombi, however, are occasionally seen. The fibrin stars of Hauser may not infrequently be seen in the bloodvessels or lymphatics or even in the œdematous interstitial tissues. The lymphatics are distended with cells, fibrin, and coagulated serum, and their endothelium shows evidence of proliferation. Phagocytic cells may be seen especially in the later periods, as may also lymphoid and plasma cells (Pratt).

In the third stage (gray hepatization), the color of the lung changes to a grayish-white, the surface is more moist, the granular plugs more prominent. The consistence of the lung is the same or slightly less than in the stage of red hepatization. A larger amount of distinctly turbid fluid may be scraped from the surface. As resolution begins the consistence diminishes, the plugs disappear and the surface is bathed in a purulent fluid—a state frequently referred to as puriform softening. Distinct abscess formation, however, seldom occurs. Microscopically, the air cells are seen to be filled with polymorphonuclear leukocytes, the fibrin becomes granular and is obscured by the leukocytic infiltration, and the red corpuscles appear only as shadows.

As resolution, frequently termed the fourth stage, advances, the fibrin and red cells are dissolved, the epithelial cells and leukocytes become fatty, phagocytic cells may become prominent and repair of epithelium evident. The lung becomes softer and gradually assumes its normal appearance. The bulk of the exudate is removed by absorption, recent investigations having shown that resolution is brought about largely by autolysis of the exudate due to a proteolytic enzyme which is much more abundant in the stage of gray than in red hepatization. This enzyme is apparently set free by the leukocytes.

While these several stages are ascribed to the course of a pneumonia it is not to be supposed that in all cases they are absolutely distinct. They merge gradually one into the other and not infrequently red and gray hepatization may be seen side by side, while puriform softening in one portion of the lung and early repair in another portion may also occur.

An idea of the distribution of the solidification and of the extent of involvement of the lung may be obtained from the following summary of Osler's Montreal statistics, based on 100 autopsies: "In 51 cases the right lung was affected; in 32 the left; in 17, both organs. In 27 cases the entire lung, with the exception, perhaps, of a narrow margin at the apex and anterior border, was consolidated. In 34 cases, the lower lobe alone was involved; in 13 cases the upper lobe alone. When double, the lower lobes were usually affected together, but in 3 instances the lower lobe of one and the upper lobe of the other were attacked. In 3 cases also, both upper lobes were affected. Occasionally the disease involves the greater part of both lungs. In a third

of the cases, red and gray hepatization existed together. In 22 instances there was gray hepatization. As a rule, the unaffected portion of the lung is usually congested or œdematous. When the greater portion of a lobe is attacked, the uninvolved part may be in a state of almost gelatinous œdema. The unaffected lung is usually congested, particularly at the posterior part. This, it must be remembered, may be largely due to postmortem subsidence. The uninflamed portions are not always congested and œdematous. The upper lobe may be dry and bloodless when the lower lobe is uniformly consolidated. The average weight of a normal lung is about 600 grams, while that of an inflamed organ may be 1,500, 2,000, or even 2,500 grams."

Accidents of Resolution.—These include organizing pneumonia, abscess and gangrene.

Organizing Pneumonia.—Occasionally the pneumonic exudate is not absorbed but remains in the air spaces. Under such circumstances the material in each alveolus becomes essentially a foreign body and the surrounding tissues inaugurate other methods for its removal. The process of removal is similar to that which takes place in the canalization of a thrombus or the removal of any necrotic material. The cells of the walls of the alveoli proliferate and new connective tissue cells in fine protoplasmic processes penetrate the exudate. These processes become canalized, form new blood-vessels, and about them new connective tissue develops, so that eventually the exudate is replaced by a new fibrovascular tissue. This new tissue gradually coalesces with the walls of the alveoli and with the interstitial tissue, so that the involved portion of the lung is eventually transformed into a dense, firm, fibrous, airless mass. Although the exudate has been removed, or rather, replaced, the area of lung affected remains functionless. The condition is termed organizing pneumonia, chronic interstitial pneumonia, induration of the lung, or occasionally, fibrosis of the lung. Under such circumstances the cut surface of the lung is reddish-brown in color with a smooth glistening surface. It is firm, dense, elastic, and can not readily be torn. Abundant pleural adhesions are usually present.

Abscess.—This is a rare complication. Laennec found but 5 or 6 cases among several hundred autopsies. Aufrecht found 3 in 253 fatal cases of pneumonia, Musser 2 in 195 cases, Pearce 3 in 121 cases. Grisolle has collected 29 cases, and Tuffier in a study of 49 operative cases found a history of fibrinous pneumonia in 23. The abscesses are usually small, though a cavity 15 cm. in diameter has been described, have an irregular sinuous outline with projecting shreds of tissue and are usually near the surface of the lung. A distinct organizing wall is seldom seen. Indeed, the condition resembles more closely necrosis in an inflamed tissue. The pneumococcus is usually present (Zenker, Pearce), though Cohn found the bacillus of Friedländer in his case.

Gangrene.—Gangrene is also a rare termination. Grisolle in his report of 305 cases of pneumonia does not note this condition and in an analysis of 70 cases of pulmonary gangrene which he collected from the literature he did not find more than 5 which could be considered as occurring in the course of fibrinous pneumonia. Aufrecht in a study of 1,501 cases of pneumonia did not meet with a single case of gangrene. The appearance of gangrene secondary to pneumonia is similar to that occurring under other conditions. Concerning the conditions which determine necrosis little is known. It is assumed that abscess formation usually precedes the putre-

factive changes. Microörganisms of putrefaction are of course present and also, as a rule, pyogenic cocci.

ASSOCIATED LESIONS AND COMPLICATIONS OF LOBAR PNEUMONIA.

Congestion of the bronchi and upper air passages, with usually catarrhal inflammation of the former, is the rule. Hyperplasia of the bronchial lymph nodes is constant. Except in the rare condition of central pneumonia the pleura is practically always involved. The exudate may be limited to the area over the inflamed lung or may be more diffuse. It varies in character from a slight clouding due to fibrinous exudate with or without punctate hemorrhages to a thick serofibrinous or fibrinopurulent exudate. Large serous effusions with more or less fibrin may occur. More rarely a definite empyema may develop.

Pericarditis, usually serofibrinous, occasionally purulent in character, is not infrequent.

Endocarditis occurred in 16 of Osler's 100 autopsies. In 209 cases of endocarditis from the literature, 54 occurred in the course of pneumonia, while in Well's collection of 517 cases there was an antecedent history of pneumonia in 22.3 per cent. The lesion is more commonly of the ulcerative type and does not differ in its pathology from endocarditis of other etiology. The aortic valve is not frequently affected.

Meningitis is not infrequent. Osler found it in 8 of 100 autopsies, Aufrecht in 7 of 253, and Pearce in 2 of 121. Councilman believes the frequency of pneumococcus meningitis is greatly overestimated and especially its frequency secondary to pneumonia. The pathology is in general similar to that of epidemic meningitis, with the exception, as Councilman points out, that purulent infiltration of the cord and brain and extension along the nerves are less marked. On the other hand, endovascular lesions are more prominent.

Less frequent complications due to the pneumoccocus are peritonitis, arthritis, otitis media, parotitis and abscesses of varied location. Occasional complications with anatomical lesions, not definitely known to be due to the pneumococcus, are arterial thrombosis, phlebitis, gangrene, and croupous or diphtheritic inflammations of mucous membranes, as of the colon, stomach and more rarely of the mouth or pharynx (Carey and Lyon).

Degenerative changes in the parenchymatous organs are usually evident. Cloudy swelling of the heart, liver, and kidneys occurs and sometimes fatty transformations of these organs. Acute nephritis, usually of the glomerular type with proliferation of the capsular epithelium, may occur; the exudative type is very rare. The spleen is often enlarged and with the lymph nodes may show proliferation of endothelial cells.

Metabolism in Pneumonia.—Atwater and Langworthy have studied 27 cases and found that "The assimilation of the nitrogenous constituents of the food in the fever period was in all cases poorer than during convalescence. In the fever period and during two or more days of convalescence an intensified destruction of the protein of the tissues took place. During the time of convalescence, when the patients began to take sufficient food, a part of the nitrogen of the food was retained. The increased outgo of nitrogen in the

urine in the period immediately after the crisis may be chiefly accounted for by the intensified destruction of proteid tissue. The ratio of the extractives to uric acid and urea was higher than normal in all cases in the fever period, and in the majority of cases during convalescence."

Cook studied 22 cases in the endeavor to establish some definite relation between the amount of nitrogen excretion and the rate of absorption of the exudate which might be of practical prognostic value. He concludes that the amount of nitrogen excreted is usually greater than that which would correspond with the amount of the original exudate. He holds that this excess is largely due to a continuation of the formation and absorption of the inflammatory exudate plus other tissue destruction. With delayed resolution the nitrogen output remains high. He believes that this indicates a continued local inflammation, and that such cases are really examples of true chronic pneumonia. When resolution is rapid the leukocyte curve closely simulates the curve of nitrogen excretion, which would seem to indicate that the white corpuscles play an important part in the production of resolution.

There is frequently a great loss of bodily weight in pneumonia. Aufrecht, who weighed his patients on admission, after the crisis, and after discharge, found that individuals ranging in weight from 130 to 150 pounds frequently lost 20 pounds during the course, although this loss was rapidly regained, and at times the original weight exceeded after convalescence.

CHAPTER XXII.

THE SYMPTOMS, DIAGNOSIS AND PROGNOSIS OF LOBAR PNEUMONIA.

By JOHN H. MUSSER, M. D.,

AND

GEORGE WILLIAM NORRIS, M. D.

THE SYMPTOMS OF LOBAR PNEUMONIA.

Incubation.—This may be short and in some cases reported by Callender ranged between two and three days. Edsall and Ghriskey's epidemic indicated that it might be less than forty-eight hours. Traumatic pneumonias are extremely interesting in this relation and the time between the injury and the onset is very brief. Thus, in one of Musser's cases, the period was less than twenty-four hours. Some authorities give a much longer interval; Penkert, for instance, places the incubation at from five to eight days.

Prodromes.—In some instances certain prodromes, such as malaise, headache, angina, gastro-intestinal disturbances, etc., may replace or precede the chill. In the appended table the frequency of various prodromes, as occurring in collected cases are recorded.

Chest pain	2,165 in 3,974	= 54.4	per cent.
Anorexia	12 in 52	= 22	" "
Headache	607 in 3,525	= 17	" "
Malaise	417 in 2,320	= 18	" "
Vomiting	192 in 1,328	= 14	" "
Abdominal pain	13 in 1,129	= 1.1	" "
Hæmoptysis	27 in 2,108	= 1.3	" "
Delirium	10 in 1,489	= 0.67	" "
Convulsions	29 in 2,691	= 1.0	" "
Somnolence	6 in 989	= 0.60	" "
Insomnia	5 in 1,001	= 0.49	" "
Tonsillitis	16 in 3,394	= 0.47	" "
Parotitis	10 in 2,655	= 0.37	" "
Epistaxis	3 in 1,208	= 0.24	" "

Undoubtedly prodromata would be more frequently encountered if their existence were more carefully investigated. Traube, who paid considerable attention to this question, held that such was the case, and further stated that in some instances definite prodromes lasting from several days to weeks occurred. Grisolle noted prodromes in 50 out of 205 cases (24 per cent.), and found that they were more common during the third and fifth decades of life. Quite often we find that the patient has had a laryngitis, coryza or bronchitis, for some time before the onset of the pneumonia. The last-named author encountered a preceding bronchitis in 19 out of 50 cases (38 per cent.).

Onset.—An abrupt onset is the rule. Among 1,276 cases with exact data, 80 per cent. began suddenly and 20 per cent. insidiously. The character of the attack which is to follow is not infrequently suggested by the manner of its beginning. Thus, a rapid onset, with a marked chill, pain in the side and a high temperature, often leads to a sthenic attack, prominent symptoms, sudden termination by crisis, and prompt resolution. On the other hand, a gradual beginning, with vague symptoms, and lower pyrexia, is often followed by a protracted course, defervescence by lysis, lingering consolidation, or untoward sequelæ.

As has been indicated, the prodromes are often in no wise characteristic of the disease, but are those common to a host of infectious fevers. Such symptoms may be referred to practically any organ or part of the body. A certain number of the patients present a mental attitude of apprehension and vague alarm, which is very suggestive.

The stage of invasion, however, is usually very characteristic. Generally a well-marked rigor is promptly followed by a rapid rise in the temperature, cough, pain and dyspnœa. The chill is often severe, lasting from one to several hours, the patient feeling very cold, shaking from head to foot, with teeth chattering, cyanosed lips and icy extremities. Chills are said to be more common during the cold months. Soon the picture changes; the patient recently agonized by frigidity feels overheated; the cheeks are flushed, often more intensely on the side corresponding to the lesion. The pyrexia may be actually not much greater than during the rigor but the patient now becomes conscious of it. The head throbs and feels as if it were bursting; the bedclothes are tossed aside. The skin is suffused with a ruddy glow, feels dry and burning to the touch; thirst appears, the eyes glisten and an expression of anxiety appears. Soon cough and pain increase. The latter, which has been lancinating, and located in the side of the chest, adds to the dyspnœa by restricting the respiratory movements and becomes more intense through continued friction of the inflamed pleural surfaces.

The exact relation of the chill to the pulmonary condition is uncertain. Some observers maintain that the disease begins in the lungs and that the chill corresponds to the time at which large doses of toxin are absorbed into the system; others hold that the rigor represents the period at which general systemic infection takes place. Opposed to the latter view is the fact that the pneumococcus can sometimes be obtained from the blood of patients without any demonstrable lung lesions or the history of a chill. Also such cases as have been reported by Syers are against it, in which all the cardinal symptoms of pneumonia, including termination by crisis, were present, but in which no physical signs could be demonstrated although repeated careful examinations were made. In other words, pneumonia is a general infection, with local manifestations in the lungs. The virulence of the toxin elaborated by the pneumococcus varies greatly in potency, and it is conceivable that in one instance a focus limited to the lungs might be sufficient to produce a rigor, while with a less virulent strain a systemic infection might be required to bring about similar results. Whichever view we are inclined to take, we must explain the production of the prodromes, particularly chill, vomiting and convulsions, by the fact that certain irritative substances are carried to the central nervous system, and that these symptoms are referable to a cerebral disturbance (Aufrecht).

The figures of 12,402 cases are as follows: of 9,851 cases, 5,731 or 58.18 per cent. had a rigor; of 2,334 cases, 703 or 30.12 per cent. had chilliness; of 217 cases, 27 or 12.44 per cent. had repeated rigors; of 1,705 cases with chill, 366 or 21.47 per cent. died; of 193 cases without chill, 27 or 14 per cent. died. Stoertz obtained a history of chill at onset in 42.47 per cent., Menge 57.6 per cent., and Morhart 41.7 per cent. of their cases. The last-named author encountered chill or chilliness in 79.8 per cent. He also found in 104 cases, that the onset occurred in the morning in 37, in the evening in 33, at noon in 23, and at night in 11. Müller found that 9 cases out of 44 had repeated chills. The presence or absence of this symptom appears to depend more or less upon the character of individual attacked. Thus, in the aged and in the subjects of chronic disease chill is less common than in robust adults.

Senile pneumonia begins very insidiously and often without symptoms of any sort until the patient is far gone. In some cases nervous symptoms are predominant, such as severe headache, delirium, mania or convulsions. The last-named are noted most often in children, but it is probable that even in them the frequency of this condition has been very much overrated. A fair proportion of the children who have been subject to convulsions at the time of onset of different infectious fevers develop epilepsy later in life; in other words, the nervous system has been susceptible from the beginning.

Earache on the side of the pneumonia is sometimes of sufficient severity to be for a time the predominant feature. This may occur independently of any local inflammation and disappears within a day or two. There is no discharge, no deafness and no perforation of the drum. Two such cases occurred in a series of 500 collected by the junior author at the Pennsylvania Hospital, Philadelphia. Meltzer has reported several cases occurring in children ranging in age from eighteen months to eight years. This condition apparently occurs only in children who have had otitis media. It is accompanied by local tenderness.

Pain at the time of onset is extremely common. It usually takes the form of "a stitch in the side," is lancinating in character, agonizing in intensity, and may be limited to the chest or radiate to other regions such as the upper abdomen. Grisolle states that chest pain occurs in 90 per cent. of the cases. It is less severe when the upper lobes are attacked, in central pneumonia, and in children. Among the last-mentioned class, however, there are frequent exceptions. Among 309 cases Grisolle found pain in 272; in 251 it occurred within the first twelve hours, in 17 in from twelve to twenty-four hours, and in 4 between the second and fourth day. Among 173 cases it was referred to the nipple region in 89, to the base of the chest in 39, below or outside of the nipple in 13, in the remaining cases it was variously distributed.

The pain sometimes occurs on the opposite side of the chest to that affected; very often, however, it corresponds to the site of the consolidation, and frequently a friction rub may be heard either directly beneath or in close proximity to the site of the lesion. It is usually increased by pressure, the patient often complaining bitterly when the region is percussed. On the other hand, firm pressure sufficient to produce immobility, such as is exerted by the entire hand or by the application of adhesive strips, often relieves it. According to Muller it is caused by a lymphangitis of the pleura, due to the invasion of the pneumococcus. Its onset is usually simultaneous with the

chill, but at times it precedes or rapidly follows the latter. The duration of the pain is variable. It may disappear within a few hours or last for several days, but it is not usually a prominent feature in the latter days of the attack. It is but little in evidence in most of the senile and asthenic pneumonias and is not noticed by delirious patients at all. Severe pain often, but by no means always, indicates a severe attack of pneumonia. Characteristic of it is the fact that it is greatly aggravated by talking, breathing, sneezing and coughing and that it is greatly ameliorated by immobilization of the chest. Occasionally it is accompanied by cutaneous hyperæsthesia. Besides the actual pain, the patient sometimes complains of a vague sensation of oppression and weight in the chest.

Abdominal Pain.—It has happened that patients have been seized with such violent abdominal pain, accompanied by rigidity of the abdominal muscles, that laparotomy has been performed for a supposed appendicitis when the peritoneal cavity proved to be entirely normal, and a subsequently manifested pneumonia turned out to be the cause of the abdominal disturbance. Chatard found abdominal pain 51 times in 658 pneumonia patients (7.7 per cent.). Griffith has reported numerous instances in children, and collected a number from the literature. The possibility of such a condition should therefore always be borne in mind, and if this is done a correct diagnosis can be made in the vast majority of cases.

Laennec noticed that the pain of pleuritis was often migratory, and states that at times "from the onset of the disease we have a stitch on the right side and a pleuritis on the left." Huss explains the occurrence of pain on the opposite side by the anastomosis which at times occurs between the right and left intercostal nerves. According to Barnard, who has dealt with the subject, Andral, Watson, and Fagge recognized the fact that disease or irritation of the pleuræ might cause severe abdominal pain. The abdominal wall is supplied with sensory nerves by the lower six intercostal nerves—the anterior divisions of the dorsal nerves. The same nerves supply a part of the parietal and diaphragmatic pleura. Irritation of any of the terminal branches may be referred to the rest. Fränzel believes that intercostal neuritis often results from pleurisy but the frequency of this seems to be doubtful. The skin over the iliac region is supplied by the eleventh nerve and it is therefore not surprising to find pain resulting from pleuritis which closely simulates appendicitis, etc.

Another explanation is also possible. Pleuritis involving the diaphragm, pericardium, or costal surfaces, may from its close proximity cause irritation of the phrenic nerve, which, according to Henle, Luscha and others, is regarded as a mixed, not a solely motor nerve. It is said to give off sensory fibers to the sub-diaphragmatic peritoneum, as well as to the pericardium, the costal and diaphragmatic pleura. Through its connection with the vagus, we can readily account for gastro-intestinal and cardiac symptoms which might otherwise seem obscure.

Rohrer considers that abdominal pain is, especially in children, often due to inflammation of the diaphragm itself. Head "believes that in certain cases there may be abdominal pain when the lung is involved without the pleura, *e. g.*, in bronchitis, tuberculosis or bronchopneumonia. He states that through the communicating branches of the seventh, eighth, and ninth dorsal nerves, which branches supply the lungs, impulses originating perhaps in a small inflammatory pulmonary focus may be carried up to the posterior

root ganglia. From the abdominal wall normal impulses pass from the epigastric and hypochondriac regions to these same ganglia. If, through the abnormal impulse coming from the lung, the ganglia have become disturbed in their function, the normal impulses from the abdomen may be distorted, *i.e.*, misinterpreted into painful impressions" (Herrick).

On the other hand, in a certain number of pneumonia patients we may have to do with actual pathological abdominal conditions, as complications such as acute peritonitis. Griffon and Bezancon have experimentally produced ulceration of the stomach in guinea-pigs as the result of pneumococcus septicæmia. Rathery has reported a case of double pneumonia with fatal hemorrhages from the intestine, in which at autopsy the entire colon was spotted with punctiform hemorrhages. Jonesco has recorded a case in which the intestine showed hemorrhagic foci without ulceration or erosion. Inasmuch as only colon bacilli could be demonstrated in the lesion, the condition seemed to be primarily toxic, with secondary infection. Rose instanced several cases of pneumonia in which abdominal pain resulted from local pathological conditions such as intussusception. It is evident, therefore, that we are dealing with a complex problem.

The onset of pneumonia is sometimes accompanied by *epistaxis*, which usually occurs in plethoric individuals. *Hæmoptysis* has been described by a number of observers. Hood's experience shows that while this symptom should make us suspicious of tuberculous disease yet it sometimes occurs purely as the result of the pneumococcus infection. The hemorrhage may be severe; in one of Hood's patients, the expectorated blood amounted to half a pint and this was repeated several times during the attack. Complete recovery ensued. On the other hand, the recent investigations of Flick, Ravanel and Irwin, at the Phipps Institute, Philadelphia, strongly suggest that the pneumococcus plays an important etiological role in the production of hemorrhage in tuberculous individuals.

Hæmoptysis occurred in 27 out of 2,108 cases collected by the writers (1.3 per cent.). The amount of blood lost may be sufficient to seriously influence the course of the disease but this is extremely rare. Aufrecht has seen but one case of large hemorrhage. The senior author has encountered the condition twice, once in a woman of forty and once in a lad of sixteen, in the course of a second attack of pneumonia which developed five days after the crisis of the first. Among 16,711 cases of hæmoptysis collected by Stricker, only 7 occurred in pneumonia.

Tonsillitis preceded pneumonia in less than 0.5 per cent. of the writers' cases. Cornil succeeded in demonstrating pneumococcus in the majority of his cases, an experience which was corroborated by that of Netter. Landgraf has reported *laryngitis* as a fairly frequent occurrence, which he considered due to excessive coughing, while Fraenkel is inclined to believe that the pneumococcus may have been the etiological factor in its production.

More or less *headache* is usually experienced at the onset; its severity often abates as the attack progresses. It is sometimes a prominent symptom in children, and according to Wells also in the aged, being frontal in such cases. Headache occurred in 17 per cent. of the writers' collected cases. It is at times sufficiently acute to suggest meningitis. *Vertigo* and *syncope* as prodromes are rare.

Convulsions occurred in 1 per cent. of the writers' cases. They are encountered in children, epileptics, neurotic individuals, drunkards and the

insane. According to Kühn, "when they appear in individuals free from nervous troubles they indicate a hereditary neuropathy."

Delirium in pneumonia may arise from various causes: fever, toxæmia, inanition, delirium tremens, cyanosis and meningitis. Among 1,048 patients, 988 were well fed, of these 175 or 17.7 per cent. died; and 60 were insufficiently nourished, of whom 15, or 25 per cent. died. Louis and Andral found delirium in 20 per cent. of their patients; Grisolle, Briquet, and Huss, in 8.12 per cent. It is said to be more common when the apices are involved. Among collected cases, 1,343 in 7,624 had delirium (17 per cent.). In the cases reported by J. McCrae, Fyshe and Ainley, 90 per cent. of the fatal ones had delirium but only 20 per cent. of the non-fatal, and more than 50 per cent. of the delirious cases, died. In 447 cases, 156 were delirious; of these 93 were alcoholics and 64 non-alcoholics. Heinze reported 317 cases, 98 of these had severe nervous symptoms, of these 40 per cent. were apical, and 25 per cent. basal cases. Regarding the number of lobes involved, Sears and Larrabee found delirium in 27 per cent. of 590 with one lobe, in 37 per cent. of 233 with two, in 35 per cent. of 99 with three, in 50 per cent. with four and in 100 per cent. with four lobes involved.

The pyrexia may increase but does not necessarily affect the delirium. The character of this symptom varies from slight incoherence to maniacal excitement. In senile and asthenic patients, it is apt to be of the stuporous muttering variety. It is said to be more common in men than in women, but if the alcoholic subjects be excluded the proportions are about equal. Its existence depends much upon individual factors and upon epidemic characteristics. It is often worse at night and sometimes only present then and during the time when the disease is at its height. The onset is often very sudden, and, as delusions are by no means rare, these patients have to be most carefully watched lest they do injury to themselves or to others. Delirium with or after the crisis occurred in 6 out of 239 of Pöhlmann's cases. In 150 cases Elsner found 4 cases of postcritical delirium, coming on from three to ten days after the subsidence of the fever; 3 terminated fatally.

Delirium due to cerebral congestion appears about the fourth or the sixth day, generally lasts only a short time and is attended by a high mortality. It may be of the low muttering or of the delirious maniacal type. In alcoholics it is apt to persist after the defervescence. Not rarely it is followed by confusional excitement with delusions of persecution, or of grandeur; the latter being associated with hallucinations, flights of ideas, and an impulse to constant movement. *Postcritical delirium* generally results from cardiac or vasomotor enfeeblement, with consequent venous stasis and cerebral œdema. This form of delirium occurs chiefly in the debilitated or the debauched. It is associated with great prostration, insomnia, hallucinatory confusion, flights of ideas, and symptoms of collapse. Delusions are usually terrifying in character—persecution, poison, sin,—but those of exaltation also occur The duration varies from a few days to months. About 84 per cent. recover (Krafft-Ebing).

An attack of pneumonia is extremely likely to precipitate mania potu in the alcoholic. This follows its usual course and very often ends in death. Of 8,998 collected cases, 383 had delirium tremens (4.26 per cent.); among 357 of these, 132 or 36.97 per cent., died. Insanity has been known to follow the delirium of pneumonia.

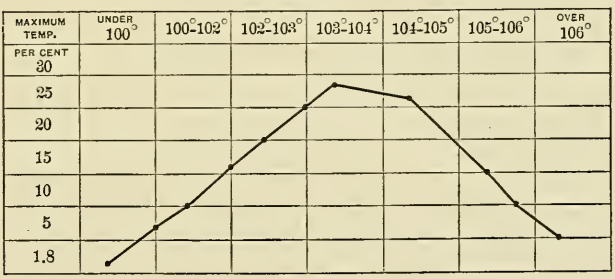
Insomnia as a prodrome occurs in a small proportion and appears throughout the disease from time to time from manifest causes. It is very probable, however, that the patient in snatching a few minutes sleep at a time, is getting much more rest than is generally realized. We do, nevertheless, see patients who remain wide awake both night and day for a considerable period. Such cases go far to justify the large doses of opium employed by some practitioners. On the other hand, it is better that the patient be alert than that he be stuporous. Sturges has written very aptly, "The best feature of his condition—which was a grave one—was his acuteness of perception and attention to his own distress." It is much easier to quiet restlessness than to arouse from stupor.

Fever.—The temperature range varies greatly. In sthenic attacks occurring in healthy adults it lies between 102° and 105° F. Many authorities consider the higher temperature as favorable, bespeaking a vigorous reaction, as opposed to those instances in which the temperature is only slightly elevated. Apyrexia is encountered chiefly among those who are enfeebled by age, dissipation or chronic disease; Traube mentions it as occurring in cases complicated by cardiac disease. Ashton and Landis found 9 with subnormal temperature among 991 cases occurring in the almshouse at Philadelphia; all died of uræmia. Noica has recorded a case in which during an eight-day attack of pneumonia, in a man aged sixty-four years, both the axillary and the rectal temperatures were persistently more than 3 degrees below normal.

In the majority of cases the fever is of the continuous type. Daily variations occur as in health, but the entire tracing is elevated several degrees above the normal. Occasionally the fever is remittent during the first few days. "Small differences are noted in mild as well as in the severe cases; especially in the latter the average slight remissions alternate not only with the greater ones, but with the intercurrent drops, and these intense, protracted cases not rarely later terminate by lysis" (Aufrecht). Lebert states that an irregular temperature curve is of favorable prognostic import.

Generally the fever rises rapidly, but not always uninterruptedly immediately after the chill. Jürgensen states that "If women are taken ill with pneumonia during the time at which their menstruation should occur, very high temperatures are usually noted." The accompanying chart graphically illustrates the maximum height of the temperature in a series of 1,443 cases (Preble).

Fig. 66.



Instead of a continuous type of fever, remissions occur during the first few days or irregularly throughout the fastigium. This may be due to infection with other organisms than the pneumococcus. A relapsing type of fever is

sometimes seen, a rapid defervescence being followed by an afebrile period lasting a variable number of hours, and terminating suddenly by a rise to the original height. This secondary elevation may be followed by the final crisis or by a second or even third pseudocrisis. Accompanying such drops in the temperature there may be no corresponding change in the character of the pulmonary consolidation. Sometimes, however, each recrudescing fastigium is accompanied by the involvement of a new area, being thus somewhat akin to wandering or migratory pneumonia. Pseudocrises are in favorable cases followed by the true crisis after a short time. In other instances the recrudescence is but the harbinger of an extension of the morbid process.

The crisis is sometimes immediately preceded by an increase of the pyrexia —critical perturbation—it being at the time impossible to determine whether such a rise heralds impending death or a rapid termination of the disease. Very high temperatures are very often fatal, but by no means necessarily so. There are records of hyperpyrexia from 107° to 113° F. followed by recovery. Ironside has reported an instance in which the temperature reached 109° F on the seventh and 109.5° F. on the fourteenth day of the disease. In the aged and in children the internal temperature may be much higher than it is at the surface; for accuracy therefore measurements should be taken in the rectum.

The duration of the fever in 1,987 cases collected by the writers was as follows:

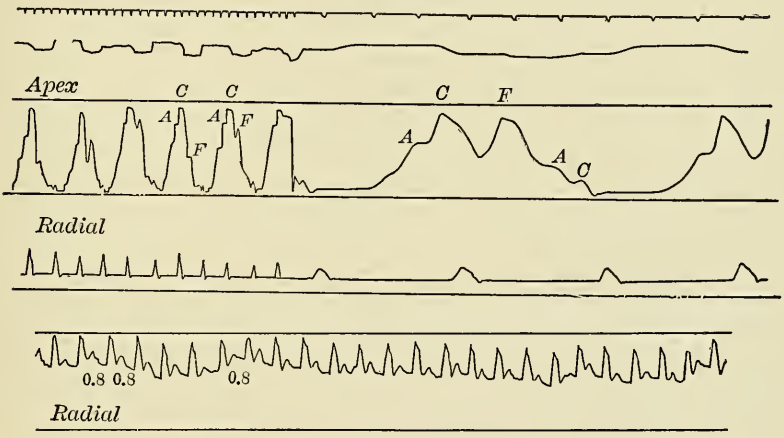
Duration of Fever.	Cases.	Per Cent.
Two days	4	0.2
Three days	32	1.6
Four days	86	4.3
Five days	195	9.8
Six days	198	10.0
Seven days	346	17.4
Eight days	280	14.1
Nine days	203	10.2
Ten days	183	9.2
Eleven days	96	4.8
Twelve days	81	4.1
Thirteen days	38	1.9
Fourteen days	74	3.8
Fifteen days	28	1.4
Sixteen days	20	1.0
Seventeen days	21	1.1
Eighteen days	37	1.9
Over eighteen days	65	3.3

Pulse.—At the onset the pulse as a rule bears the usual relation to the temperature but falls behind the respiratory rate. It tends to be more rapid in children than in adults, in women than in men, and in persons of small than of large stature. At the beginning of a sthenic attack it is full and bounding, assuming the type which was formerly considered a signal for venesection. Gradually, as the disease progresses, it becomes smaller and weaker. This is particularly the case if much lung tissue is consolidated, the right heart overtaxed, and in patients who are markedly toxic. Sometimes the pulse is much affected by the respiratory movements. The following table, based upon 1,064 cases, is taken from Preble:

	Per Cent.
Below 100, maximum rate	5.3
100 to 110	11.5
110 to 120	13.3
120 to 130	27.0
130 to 140	13.5
140 to 150	11.7
150 +	7.8

The pulse rate is regarded by many as a reliable prognostic sign; thus Griesinger states that of those with a rate higher than 120, over one-third die. Sears and Larrabee found that the death rate bore a direct relation to the rapidity of the pulse and the amount of urine voided. Certainly the mortality increases very rapidly when the pulse rate passes 125, a figure which of course does not refer to children, in whom a range of 120 to 200 is not so very rare. But we must not place our estimation upon the rapidity alone; the rhythm, volume and tension are of even greater importance. Any deviations from the normal in respect to the character of the pulse call for the most careful attention; and, as a general rule, the earlier in the course of the disease they appear, the less favorable is the outlook. "If the evening pulse takes on the hesitating character shown in the sphygmogram by a broken

Fig. 67.



ascending line, the prognosis is grave. It coincides with feeble arterial tension, and cardiac failure due to myocarditis" (Carriere). "In all cases of acute lobar pneumonia that I have met, when the pulse showed even an occasional irregularity before the crisis was reached, death supervened. I have not found a single exception to this rule for over ten years, and while extended experience may prove it fallacious, irregularity of the pulse with pneumonia must, at all events, be looked upon as a most serious symptom. In pneumonia the amount of arterial pressure, the rate of the pulse, and its rhythm, are each of them among the most important indications we possess. Within a few hours after a rigor the fatal termination may be too plainly foretold by the character of the pulse. I have rarely seen an adult with a pulse over 140 recover" (Mackenzie).

The foregoing are statements to which doubtless some would take exception, but coming from such an authority as Mackenzie they possess much

weight. There can be no doubt that if the pulse were studied routinely by such instruments as Mackenzie's clinical polygraph or Jacquet's cardiosphygmograph, which indicate so much more as to the state of the heart muscle than the sphygmograph, and if the results thus obtained were interpreted not in their own light alone but in correlation to the data concerning the blood pressure, we should have much more accurate and satisfactory knowledge.

The foregoing sphygmogram was taken with a Jacquet instrument, on the eighth day of a severe, massive, croupous pneumonia; in a man aged thirty years. The latter half of the upper tracing shows the speed of the rollers increased thus producing a magnification of the pulse curves. The second tracing is from the radial artery and has been added since the radial tracing on the first strip was incompletely reproduced.

The *first line* in the tracing represents the apex beat; the *second* the jugular and carotid pulses; the *third*, the radial. At the time these tracings were made the patient was in an extremely precarious condition, in which he remained for several days, eventually recovering. The pulse was 98; temperature, 100° F.; respirations, 45. There was marked cyanosis; the external jugulars were enormously distended and visibly pulsating. The *heart* was considerably dilated and enlarged, especially to the right, but there was marked accentuation of the pulmonary second sound. There was a systolic murmur at the apex, at which point a forcible impulse could be seen and felt.

Cardiosphygmogram.—The radial impulse is very dicrotic; the rate rhythm, however, is fairly regular, successive ventricular systoles following each other at intervals of 0.8 second. The jugular and carotid waves are both very large, owing to venous stagnation, and vascular relaxation respectively. The regular alternation of large and small waves is apparently due to the effects of respiration, the pulse rate being about twice that of the respiration. This was brought about partly by the collapse of the veins during forcible inspiration. The time elapsing between the beginning of auricular and of ventricular systole is slightly less than 0.2 of a second, conductivity being therefore normal. The filling wave which follows the carotid is very large, and occurs very quickly after the latter, bespeaking marked venous stagnation in the right heart. The auricular wave is well marked, showing that the auricle contracts with considerable force.

A cardiosphygmogram taken three days later, after the patient had had his crisis, showed a marked lessening of dicrotism in the radial artery and much less venous stagnation; the jugular pulse wave being much smaller, the filling wave being noticably less in evidence and occurring later in the cardiac cycle.

The normal relation of the respiration to the pulse is 1 to 4.5; in pneumonia it may be 1 to 3, 1 to 2, or even 1 to 1. In doubtful cases, with equivocal physical signs, such a disturbance of the ratio is often very suggestive of this disease. The postcritical pulse is slow unless cardiac weakness is very great; in some cases an actual bradycardia is encountered.

Blood Pressure.—Fraenkel found in the majority of his cases moderate but constant hypotension, with the Gärtner tonometer. In about one-third of the cases this was not the case. Occasionally in sthenic cases tension was increased for the first day or two. Norris found no constant relations, nor did he observe, except in one case, a critical fall in pressure such as has been

described by Zadek, Christeller, and Ekgren. Potain found normal pressure, Cook and Briggs, Gilbert and Castaigne, hypertension; Hayaski, Kaufmann and de Bary, and Torchio found hypotension. Gigliosi, in 50 cases measured with the Riva-Rocci instrument, encountered slight pressure in favorable cases, while a sudden fall occurred coincidentally with cardiac dilatation. Neither Hesen nor Mosen noted a fall of pressure at the time of crisis. Janeway found considerable daily variation, the pressure charts being, nevertheless, distinctly valuable therapeutic guides in a general way rather than from the absolute height of the readings. "When one pictures the possible causes for variation in lobar pneumonia, the difference in individual reaction to toxæmia, in extent of lung tissue involved, the motor restlessness of some patients, the urgent dyspnœa of others, and the great likelihood of an asphyxial rise of pressure when cyanosis is extreme, there is little wonder at the somewhat discordant results" (Janeway).

Another cause for discrepancy lies in the fact that a number of the above-mentioned observers used the Gärtner tonometer, an unreliable instrument, which becomes doubly so in case of venous stasis, cyanosis and variation in the capillary tension.

Certainly it would seem that the systematic observation of the blood pressure, especially when the results are considered in correlation with the pulse rate, temperature and respirations, should prove a useful guide in anticipating collapse, which often appears unexpectedly.

The Heart.—Examination of the heart itself, aside from the rate, may reveal nothing abnormal but very often, especially during the latter part of the attack, we find functional murmurs either with or without dilatation. In this latter condition the right side is the greater sufferer by reason of the obstruction to the pulmonary circulation. The mere fact, however, that the area of dulness extends beyond the right sternal border need occasion no alarm unless there be other evidences of cardiac weakness, as this may be produced by retraction of the lung. According to Jürgensen, it occurs as the result of shallow breathing, which, owing to lessened inflation of the lung, imposes less counter force to the elastic tissue, thus permitting the elastica to retract the overlapping pulmonary margins. A second cause for apparent dilatation may arise from consolidation of the left lung, which tends to displace the heart to the right and a similar result may be caused by a left-sided pleural effusion. If the right middle lobe is infiltrated it may be almost impossible to outline the right cardiac border even by auscultatory percussion. In some severe and fatal cases no cardiac dilatation may be demonstrable.

Functional murmurs are common; they may arise from relaxation of the myocardium, from the rigidity imposed upon the large vessels at the base by consolidation of the surrounding lung tissue, or from changes in the composition of the blood. Organic murmurs may result from preëxisting valvular disease or from acute endocarditis; the possibility of the latter should always be borne in mind. Of great importance is the character of the second sounds at the base. The pulmonic sound is generally accentuated, sometimes reduplicated. The disappearance of an accentuation is often a sign of ominous import, pointing to the fact that the overburdened right heart is giving way and an acute dilatation impending. When the upper lobes are the seat of the disease, the character of the second sound is less reliable, for the reason that a neighboring consolidation may cause a weak sound to seem

clear and intense. As in other forms of pulmonary infiltration, the heart sounds are often transmitted very distinctly to distant parts of the chest.

Cardiac weakness in pneumonia may arise from a number of causes; the commonest and most important of these are toxæmia, extensive pulmonary consolidation and hyperpyrexia. The first of these may result either from a direct action of the poison upon the muscle itself—cloudy swelling, myocarditis—or indirectly through a paresis of the vasomotor system. Romberg and Paessler have shown that heart weakness in animals in the course of septicæmia due to the pneumococcus, *B. pyocyaneus* and *B. diphtheriæ*, is only apparent, and that if the vasomotor system can be stimulated, the symptoms of cardiac enfeeblement disappear. Of course, conditions in the human being are more complex by reason of the obstruction in the pulmonary circulation but it is only reasonable to assume that within certain limits the conditions are analogous.

Sudden syncope may occur at any time in the course of the disease, although this is rare, occurring according to Aufrecht in about 0.5 per cent. The pulse is rapid and small in volume, and the attacks, even in patients who recover, may last six or even twelve hours. The usual symptoms of heart weakness, including cyanosis, dyspnœa, cold extremities and nervous derangements, occur. Critical collapse, or at least a tendency toward it, is quite common. It sometimes appears at the beginning of the crisis, more rarely in the midst of it. It is accompanied by chilliness, cold perspiration, dyspnœa, cyanosis, a weak rapid irregular pulse, mental incoherence and subnormal temperature. With judicious stimulation these attacks are usually passed in safety, although death in the course of them is by no means unknown. Collapse coming on a day or two after the crisis is much more grave, being usually an indication that the myocardium has sustained serious damage. It sometimes happens that the patient falls back dead, after sitting up the first time, although there had been no indications of the precariousness of his condition. In such cases one naturally thinks of an acute cardiac dilatation or a pulmonary thrombosis as the cause of death.

Respiration.—The character of the breathing is very significant, often absolutely diagnostic of the disease. The respirations are short, shallow, voluntarily and involuntarily restricted, and accompanied by movements of the alæ nasi. Later on as pain diminishes and involvement becomes more extensive, they increase in depth, become more labored and the accessory muscles are called into action. The rapidity is due in part to the pain and fever, in part to the amount of lung involvement, and in part to the toxæmia or cyanosis. Washbourn has shown that mice infected with the pneumococcus are dyspnœic although pulmonary consolidation is absent. Owing to the pain the respirations are not sufficiently deep; hence carbon dioxide accumulates and adds to the already overstimulated respiratory centre. The truth of this is shown by the fact that an injection of morphia which allays the pain will often cause the disappearance of the cyanosis and an alleviation of the dyspnœa. The causes mentioned contribute to increase the respiratory rate far beyond the normal, in relation to the pulse and temperature and this increase may persist after the crisis, when the last named have fallen to normal or below it.

The gravity of the respiratory condition is not to be reckoned by the rate alone. Thus, when pain is a prominent feature, the breathing may be very rapid, and yet the patient is in much less danger than when the actual c_unt

is lower with cyanosis, distended jugular veins and cold extremities present. The "expiratory grunt" is a sign of great diagnostic importance, especially in children. It may occur although pain be absent.

The rate in adults usually ranges between 24 and 48 per minute; only 11 per cent. of Gerhardt's cases had respirations over 40 per minute. While an exact danger line is hard to draw, respirations of 50 or more, unless due to some definite cause such as great pain, mental excitement, pleural effusion, etc., are usually a cause for apprehension, especially with lividity and marked movements of the alæ nasi. Respirations of 90 to the minute have been recorded. Jürgensen has, in severe cases of arteriosclerosis, seen the respirations more rapid than the pulse. In children the range is generally between 40 and 50. The senior author has seen a child aged two and one-half years, with pneumonia, breathing 120 times to the minute. The following table (Sears and Larrabee), based upon 740 cases over fifteen years of age, exemplifies what has been stated:

Number of Cases.	Respiration.	Per Cent.
45	Below 30	6.2
200	30 to 40	27.
288	40 to 50	39.
107	50 to 60	14.4
82	60 to 70	11.
18	Over 70	2.4

Dyspnœa.—Dyspnœa is rarely dangerous *per se* unless there exists a profuse bronchial catarrh, or œdema of the lungs. It was a prominent feature in 71 out of 489 of Musser's cases (15 per cent.). As would be expected, dyspnœa is urgent in cases complicated by large pleural effusions, emphysema, scoliosis, etc., in which expansion of the uninvolved lung tissue is restricted. *Cyanosis* occurred in 119 of 1,239 of the writers' cases (9.6 per cent.); it is usually seen with large areas of consolidation, enfeebled pulmonary circulation, toxæmia or œdema of the lungs.

Cough.—Cough is nearly always present, the exceptions usually being in the aged, in those complicated by delirium tremens, in apical lesions, and the pneumonias secondary to circulatory disease, typhoid fever and puerperal sepsis. Cough was a prominent feature in 1,626 out of 2,534 collected cases (65 per cent.). Jürgensen very aptly remarks that "it is rarely useful, always troublesome, sometimes dangerous." It appears early in the course of the disease, usually with or soon after the chill. It precedes the latter symptom when bronchitis antecedes the pneumonia. At first it is unproductive, paroxysmal and extremely painful. Later on, expectoration appears and the cough may partially abate; often, however, the paroxysms increase in severity and duration as the attack progresses, severely taxing the patient's strength by preventing sleep, the nervous system by excruciating pain, the right heart by increased pressure, and the respiration by muscular stiffness and fatigue. The sudden disappearance of cough is an unfavorable symptom, not rarely heralding the onset of exhaustion, stupor or coma.

Sputum.—The sputum is at first scanty, frothy, white or faintly streaked with blood, and may contain diplococci. In the course of a few hours it becomes rusty or brick-dust in color, as the result of an increased admixture with blood, which is uniformly mixed throughout a glairy menstruum. Microscopically many crenated red blood corpuscles are seen; the color is due in

part to these and in part to dissolved hæmoglobin. To the naked eye it has a vitreous, glairy, semitranslucent appearance. Later, leukocytes and shreds of fibrin cause it to become opaque. Casts of the bronchioles and Curschmann spirals are also encountered. Sometimes a green color is met with either in the early or late stages of the disease, a condition which Nothnagel considered due to changed bile pigment. According to v. Jaksch, hæmoglobin and bilirubin are changed to biliverdin in the lungs. On the other hand the green hue may, as Rosenbach has pointed out, be produced by microörganisms such as the *Micrococcus chlorinatus*. In the course of time the sputum becomes less viscid and more profuse, the color changing from a pink to a citron yellow or saffron; gradually erythrocytes and leukocytes decrease, as do also the color and the amount of the alveolar epithelium; changes which become more pronounced during the stage of resolution.

The amount is small, rarely exceeding 2 ounces per day. According to Osler it ranges from 150 to 300 cc. "Huppert and Riessell found, in a pneumonia of the entire left lung, that the maximum daily amount of sputum expectorated was 67.3 gm., with 5 gm. of dry matter. Renk found, in a case of pneumonia at the middle of the attack, a daily amount of sputum of 26.0 gm. with 23.66 gm. of water" (Aufrecht). In other words only a small part of the inflammatory exudate of the lungs is coughed up, the greater part being absorbed.

During the febrile stage the sputum contains large numbers of microorganisms, which rapidly decrease in number after the crisis. The duration of the attack can at times be forecast to a certain extent by the nature of the organisms found; thus, a pneumonia due to the influenza bacillus, or in which there is mixed infection, runs a more protracted course and instead of terminating by crisis, does so by lysis, and is more apt to be followed by delayed resolution, suppuration, gangrene or other abnormality. The identification of the pneumococcus in the sputum is usually easy and should be routinely attempted. The tubercle bacillus is to be sought for in suspicious cases by the ordinary method. The number of pneumococci demonstrable in the sputum does not bear any constant relation to the severity of the attack. Stuertz has made a study of the virulence of the organisms in the expectoration by injecting mice and has shown that the crisis is not due to decrease in the virulence. Exacerbations and relapses, however, are accompanied by increased virulence. He believes that such events may be forecast by inoculating mice at regular intervals throughout the attack.

The sputum is sometimes very hemorrhagic. This has been observed in tuberculous cases (Walshe), in heart disease (Huss), in lobar pneumonia produced by the typhoid bacillus and in traumatic pneumonia. Leichtenstern suggested that atheroma of the pulmonary artery may cause the so-called "hemorrhagic pneumonia." Grisolle gives the following data as to the time at which the rusty sputum appeared in 131 cases. It will be noticed that it appeared within the first two days in 60 per cent., and within the first four days in 80 per cent. of the cases: First day, 45; second day, 31; third day, 14; fourth day, 14; fifth day, 11; sixth day, 6; seventh day, 5; eighth day, 2; eleventh day, 2; twelfth day, 1.

In 195 cases collected by the senior author, rusty sputum was present in 73 (37 per cent.), absent in 40 (20 per cent.), unrecorded in 82 (43 per cent.). In 43 cases examined microscopically the following organisms were noted: diplococci 17, streptococci 10, staphylococci 7, influenza bacilli 3, tetrads 4,

Wolff found the diplococcus in 66 out of 70 cases examined, the Friedländer bacillus was encountered only three times, and once neither organism was found. Among collected statistics: of 3,286 cases, 1,627 or 49.51 per cent. had rusty sputum; of 1,406 cases, 203 or 14.44 per cent. had mucopurulent sputum; of 5,249 cases, 70 or 1.33 per cent. had bloody discharge or free hemorrhage; of 25 cases, 19 or 76 per cent. had casts of air vesicles; of 2,184 cases, 361 or 16.53 per cent. had no sputum. Hemorrhagic infarction of the lung gives a sputum similar to lobar pneumonia but even here the expectoration is more bloody, less viscid and lacks the bright-red color. "Prune juice" sputum has been attributed to lessened coagulability of the blood and a diminution of cardiac power, having therefore been regarded as an unfavorable symptom which sometimes precedes an œdema of the lungs. Williamson states that pneumonia due to the Friedländer organism is to be suspected when the mucus is "intensely mucoid, ropy and stringy, so that when lifted on a knife blade or similar instrument it can be drawn into long threads. This is not remarkable when we remember the peculiarity of the Friedländer organism in the culture media." When jaundice is present the sputum may be bile stained and have a bitter taste.

As to the chemical composition of the sputum, all investigators are agreed that the albumin content is high, owing mainly to the large amount of blood which it contains. After the crisis the amount of albumin is markedly decreased. Bussenius was able to demonstrate glucose in the expectoration of a diabetic woman who had developed pneumonia. "The basis of the pneumonic expectoration is water, albumin, mucus, fat and salts, with which the other more adventitious elements are mixed. The percentage of water to the solids bears a close relation to the proportion of water in the blood. Albumin forms about 3 per cent. of the sputa. The viscidity depends upon the mucus, which is present to the extent of about 1 per cent. It is supplied by the inflamed bronchial mucous membrane. The salts constitute about 0.8 per cent. of the expectoration, and of these the chlorides form about one-half. The expectoration is usually neutral or slightly alkaline, rarely acid" (Wells).

Sometimes expectoration is entirely absent. This occurs notably in children who swallow it, and in delirious or stuporous patients, who fail to cough it up. It is decreased in pneumonia affecting the upper lobes. Bouillaud explains this by the fact that the exudate in the bronchioles of the upper lobes is less likely to be dislodged by breathing and coughing. Aufrecht believes that it is due to "the same causes as is the condition of the alveoli which are less completely filled in pneumonia of the upper lobes during the stage of red hepatization; namely, to a diminished hyperæmia, or, to be more exact, a diminished amount of bleeding into the alveoli of the upper lobes during the stage of inflammation. The result of this is that the accompanying secretion of the finer bronchi is less than in pneumonia of the lower lobes. More difficult to explain is the frequent absence of sputum and especially of bloody sputum, in pneumonia of the lower lobe, which occurs in the course of delirium tremens, in insane patients, in the aged, and in the course of pneumonia after acute diseases. We can only mention the hypothesis that in such cases a stasis follows in the capillaries and veins as a result of disease of the alveolar epithelium, and produces a migration of the white corpuscles into the alveoli; that is to say, the gray hepatization occurs so quickly that the intermediate stage—red hepatization, due to the

migration of the red corpuscles—lasts too short a time to produce bloody sputum."

The demonstration of Fraenkel's pneumococci in the sputum of patients suspected of having pneumonia may be considered satisfactory evidence that such is the case; particularly if they are found in large numbers and in the central parts of washed sputum. In cases in which the sputum is secondarily contaminated in the mouth the organisms found are much fewer in number, and located peripherally. The evidence obtained from a study of the expectoration is, of course, not of such positive nature as that derived from a blood culture, but it is for obvious reasons much quicker in its results and more generally applicable.

Method.—The sputum for examination should be collected in a regular sputum cup, or in a wide-necked bottle, and when possible a liberal quantity obtained. Neither water nor disinfectants should be added. A smear is made in the usual manner by rubbing the sputum for a time between two cover-glasses. The diplococcus of pneumonia stains well with Gabbett's methylene blue solution, but its characteristic biscuit-shaped contour is better brought out by Bismark brown. When thus stained each coccus is seen to be surrounded by a narrow hyaline space, bounded by a faint marginal capsule. Encapsulated pneumococci are seen with difficulty. The staining of the capsule is best accomplished by the following method: The smear is placed in a 1 per cent. solution of acetic acid for one or two minutes. The excess of the acid is then removed with a pipette and the slide dried in air. After this it is placed for a few seconds in saturated aniline water and when dry, examined. The microscope reveals elongated lance-shaped cocci, generally arranged in pairs, with their bases approximated, and characteristically encapsulated.

If desired, the double-staining method of Wolf may be employed. The dry smear is stained in aniline water saturated with fuchsin, and then placed for one or two minutes in a diluted aqueous solution of methylene blue. The cocci are thus stained blue, the capsule rose color, and the body of the preparation a bluish-red. The Friedländer pneumobacillus may be stained by the same methods as the pneumococcus and also shows capsule formation.

Posture.—The posture assumed by the pneumonia patient varies. Most often the dorsal decubitus is chosen and the affected side is usually avoided on account of pain and tenderness; the sitting posture is rarely assumed except in case of apical involvement, in which the lateral position is also occasionally adopted. The reason of this is that in basal lesions the movements of the heart, the diaphragm, and the lungs themselves, are least encroached upon when the consolidated portion falls back against the posterior thoracic wall.

Perspiration.—Perspiration may occur at any time during the attack of pneumonia. It is most common during or after the crisis, more frequently seen in children and in young adults, and in uncomplicated, sthenic cases; occasionally it is very profuse. Sweating also occurs during the last few hours of some fatal cases as the result of vasomotor paralysis. Sudamina may occur upon the reappearance of sweating after its absence during the height of the disease.

Herpes.—This is a very common and often diagnostically significant symptom. It generally appears upon the lips, or at the angles of the mouth or nose, but may be about the ears, eyes, chin, anus, genitalia, legs, or in fact any part of the body. The vesicles may appear with the prodromata. Aufrecht mentions an instance in which they preceded the pneumonia by

two days. Generally, however, they appear about the third day of the disease. Geissler, who has investigated this in 421 cases, among which there were 182 cases of herpes, gives the following data as to the time of onset: On the first day of disease in 1, second in 18, third in 66, fourth in 41, fifth in 20, sixth in 8, seventh in 4, eighth in 5, ninth to tenth in 2, and on the eleventh or later in 8. In 79 per cent. of Riehl's cases herpes appeared between the third and fifth days; the earliest on the second, the latest on the twenty-sixth. The eruption of the vesicles may be preceded by a chill but this is by no means always the case. The condition is easily overlooked because in some cases only a single vesicle appears. The number may range to many dozen. Often they are overlooked because they appear just within the nose. These facts probably account in some measure for the great discrepancy in reports as to their frequency, although there is no doubt that they are more common in certain years and epidemics. Herpes has been reported as follows; Geissler 43 per cent., Bleuler 43 per cent., Stoertz 20 per cent., Lebert 13 per cent., Schapira 29 per cent., Drasche 40 per cent., Riehl 27 per cent., Morhart 37 per cent., Pye-Smith 12 per cent., Townsend and Coolidge 7 per cent., Wunderlich 50 per cent., Hawkins 20 per cent., etc.

Riehl has found the following age distribution in 127 instances of herpes among 481 pneumonias:

14 to 20 years	36	cases of herpes.
20 to 30 "	55	" "
30 to 40 "	18	" "
40 to 50 "	6	" "
50 to 60 "	9	" "
60 to 70 "	4	" "
70 to 80 "	1	" "

In 90 per cent. of the cases the eruption appeared in the distribution of the trifacial nerve; in 42 per cent. about the lips. It was formerly supposed that herpes arose as the result of a disordered condition of the blood, but the very interesting investigations of Howard[1] seem to have definitely established the etiological factor to be a neural one located in the nerve, skin and posterior spinal ganglion corresponding to the nerve in the distribution of which the eruption appeared. When they appear in the distribution of the fifth nerve, the lesion is in the Gasserian ganglion. The pathological changes consist of congestion, hemorrhage, cellular infiltration, degeneration of the ganglion cells, and are probably the result of the toxins.

Since the appearance of Geissler's article it has been believed by many that the appearance of herpes was a favorable prognostic sign. An examination of the literature reveals the following reports:

Observer.	With Herpes.	Mortality.	Without Herpes.	Mortality.
Geissler	182	9.3 per cent.	239	29.3 per cent.
Schapira	173	35.7 " "	38	34.21 " "
Stoertz	52	9.6 " "	234	17.9 " "
Morhart	63	8.9 " "	108	7.4 " "
Baeck	35	4.16 " "	49	14.0 " "

Pöhlmann did not find herpes in any of his fatal cases. Among the writer's collected cases, 943 out of 4,447 had herpes (21.21 per cent.).

[1] *American Journal of the Medical Sciences*, February, 1903, p. 256.

Of 396 with herpes, 43 or 10.86 per cent. died; of 239 without herpes, 70 died (29.29 per cent.). Of 111 autopsies, 103 had no herpes (92.79 per cent.), while 8 had herpes (7.21 per cent.). Among 434 cases of pneumonia, Pye-Smith found 53 with herpes, of which 47 recovered. In one of Morhart's cases the eruption was situated on the cornea of the left eye, in another on the sternum. The site of the pulmonary lesion bears no constant relation to the location of herpes.

Urine.—This is decreased in quantity, abnormally concentrated, being therefore "high colored," increased in specific gravity, and often irritating. The latter quality may be manifested by burning pain on or after micturition; and in women with perineal lacerations in whom coughing and weakness may produce incontinence, excoriation of the skin. The quantity voided is about one-half the normal, remaining at this level while the fever lasts. Entire suppression is rare. The junior author saw a middle aged man with pneumonia, the right upper and middle lobes being involved, in whom there was absolute anuria for three days during the febrile period. Beyond somnolence, there were no symptoms of uræmia. Crisis with perfect recovery followed. Epicritical polyuria is sometimes seen. The darkened color is due in part to concentration, and in part to increased urobilin, resulting from the destruction of erythrocytes. Uric acid and urea are increased. The urea is increased after the crisis, according to Scheube: first, because the disintegration of albumin probably continues for a time after the pyrexia; secondly, increased diuresis tends to flush accumulated urea from the system; and, thirdly, resorption of the pulmonary exudate produces increased albuminous material which is mainly eliminated by the kidneys.

The chloride excretion is greatly diminished, and quite often entirely suppressed, supposedly due to the fact that precipitation of albumin in the pulmonary exudate ties up large quantities of these salts. This explanation is unsatisfactory inasmuch as it has been shown that consolidated areas show "an average of 1.69 per cent. of sodium chloride, while normal lung shows 1.4 per cent.," too slight a difference to account for the phenomenon (Preble). Roehrmann has shown that the statement made regarding abnormally low absorption from the intestinal tract is equally fallacious. According to von Limbeck and Moraczewski, the blood of pneumonia patients is also deficient in chlorides. Further evidence against the diminution of urinary chlorides being due to an increase in the sputum and inflammatory exudate was pointed out by Traube, namely: that this condition occurs in other febrile affections in which there is no pulmonary exudate; that the amount of chloride suppression bears no relation to the amount of consolidation; and finally, that during beginning resolution the excretion may be just as low as during the fastigium. Aufrecht believes that during the fever the products of katabolism are taken up by the circulation; only a part of them, however, are immediately transformed into their final products, the remainder being retained in the body by combining with the sodium chloride in the blood plasma.

Hutchinson has shown that the retention of sodium chloride, the average amount being 29 gm., persists until a day or two after the crisis, when increased excretion occurs. The degree of chloride retention bears no relation either to the height of the fever, the amount of lung involvement, or the presence of albuminuria. The other solid constituents of the urine are not decreased in pneumonia.

The amount of chlorides excreted in the saliva is relatively large, but the actual daily amount is small. Hutchinson believes that this passage of the chlorides from the blood into the fixed tissues is due primarily to the exudation of water. The following table shows the condition of chloride excretion in 436 cases of pneumonia:

	Ashton and Landis.	Musser.	J. McCrae, Fyshe and Ainley	Haddon, Mackenzie and Ord.	Total.	Per Cent.
Chlorides normal	18	6	4	56	84	19.2
Chlorides decreased	66	18	9	139	232	53.2
Chlorides absent	72	20	3	25	120	27.5

Of the 25 cases with chlorides absent, 7 died (28 per cent.), of 139 cases with chlorides diminished, 22 died (15.83 per cent.), and of 56 cases with chlorides normal, 7 died (12.5 per cent.). The chloride excretion in pneumonia has no value from a prognostic standpoint, although it was for a time believed that its reappearance after an absence heralded the onset of the crisis. As a diagnostic aid it is also of but little value, although this phenomenon does occur more constantly and to a greater extent in pneumonia than in other conditions. Of course, in a febrile case with normal excretion, we might not unreasonably be lead to suspect that we were dealing with a disease other than pneumonia.

Pick has called attention to the fact that in some cases the acidity of the urine may be decreased even to the point of actual alkalinity immediately after the crisis. The observation has been corroborated by a number of investigators. One would naturally expect that the increased destruction of leukocytes which is supposed to occur at this time would tend to have the opposite effect. Pick encountered this condition in 31 out of 38 cases, and considers it due to the absorption of alkaline salts from the resolving exudate. The urinary sulphates are decreased in pneumonia, the phosphates are increased during the fastigium.

It has been stated by numerous observers that peptone appears in the urine in a considerable number of cases. This has been interpreted as showing that the exudate is being absorbed. Later work seems to show that the substance hitherto regarded as peptone is really a mixture of albumoses and peptone. The researches of Krehl and Matthes indicate that the chief constituent is deutero-albumose, but Ito states that true peptone is encountered with comparative frequency. The value of such findings has more of a scientific than a practical value. As has been intimated, the occurrence of these substances has been supposed to indicate a disintegration of albumin.

As in other febrile disorders, *albuminuria* is common in pneumonia. This is considered under the renal complications. Among the abnormal substances in the urine we have, as in other fevers, an increase in acetone. V. Jaksch has shown that this is also found in the expired air in some cases. The diazo reaction is more common than in other fevers, but less so than in typhoid fever. It has no practical significance. Among collected cases, 35 in 366 gave this reaction (0.95 per cent.). Indican was found in 10 of 366 (0.27 per cent).

As regards *cryoscopy*, F. E. Schmidt has found that (1) the freezing point of the urine is considerably lowered and (2) to a greater extent than the

concentration of the urine can account for; (3) the lowered freezing point is not due to abnormality of the chloride constituent but to metabolic molecules excreted.

The Spleen.—As in other infectious fevers, enlargement of the spleen occurs in pneumonia. This was first pointed out by Friedreich who found, "considerable swelling of the spleen during the first few days," which later "developed to such an extent that it protruded below the costal arch, and could be clearly palpated," being about as large as the splenic enlargement of typhoid fever, from which, however, it is distinguished by the fact that it assumes the normal dimensions as soon as the fever disappears. This form of splenic enlargement is due to hyperplastic swelling of the parenchyma and usually appears before consolidation of the lungs is far advanced.

Among the cases collected by the writers, splenic enlargement occurred clinically in 791 out of 1,416 cases (34.6 per cent.), and postmortem in 147 out of 292 autopsies, about 50 per cent. Acute parenchymatous splenitis occurred 140 times in 293 postmortems (47.7 per cent.) and chronic splenitis, once in 173 (0.57 per cent.). Fraenkel found the spleen enlarged in about 15 per cent. of his cases, and E. Fraenkel and Reiche, in 40 per cent. of their fatal cases. The fact that the splenic enlargement often indicates severe attacks is also substantiated by Rychner, who, in 616 cases with a general mortality of 25.7 per cent., found the death-rate in the patients with enlarged spleens more than doubled (55.4 per cent.). He also found that only 17.9 per cent. of these cases ended by crisis, and that splenic enlargement was twice as common in men as in women, and rarer in the late adult and advanced than in the early years of life.

Splenic enlargement does not seem to bear any definite relations to the character of the onset, chill, etc., but it does seem to be more or less proportionate to the duration of the fever, hence its greater frequency in cases defervescing by lysis. Steven in 120 autopsies found cloudy swelling in 58 and normal spleens in 15. Jürgensen in 73 postmortems found splenic changes in the majority, mostly in the nature of enlargement.

Adenitis is also encountered; Manchen found enlargement of the lymph nodes quite frequently. It was found in nearly one-fourth of the cases at the Würtzburg clinic, occurring 77 times in 259 cases, with the following distribution: inguinal 36, cervical 14, and both 13.

The Blood.—During the febrile period the red corpuscles are practically normal. During the crisis, in the majority of cases, they diminish in number. After the crisis they may rise again to normal within a few days or remain down for a few days. Nucleated red corpuscles are rarely present, except in cases of delayed resolution, and then only in small number. They may also be present in other complications. The hæmoglobin behaves much as the red corpuscles. According to Boeckmann, the erythrocytes are in inverse proportion to the temperature, while the number of leukocytes tends to be directly proportionate to the same. V. Jaksch has corroborated Tuman's statement that in children the proportion of leukocytes to erythrocytes ranged from 1 to 40 or 70. In patients with cyanosis the red cells may be increased. The amount of post febrile anæmia is usually slight, the hæmoglobin being slightly more decreased than the corpuscles. According to Cabot, the specific gravity of the blood is high and in children falls with the temperature.

In the large majority of cases there is a marked increase in the number of leukocytes, but cases occur in which there is no increase, and these are not infrequently fatal. In children the leukocytosis may be very marked. According to Cabot, when either the patient or the disease easily gains the upper hand there is no leukocytosis, or only a slight one; but in the much larger class of cases in which the struggle is a fierce one, leukocytosis appears, whichever way the battle results. When the patient is already ill from some other morbid process such as typhoid fever, variola, alcoholism, or chronic disease, there is no increase in the white cells. In these cases the absence of leukocytosis is not necessarily an unfavorable sign. Thus, Scott has reported 10 cases of pneumonia complicated by typhoid fever; in only 1 of these, in which parotitis was an additional complication, were the leukocytes above 10,000. Wilson found that the injection of antipneumococcic serum produced a marked increase in the number of white corpuscles, and Hare has pointed out that leukocytosis is prevented by antipyretics but not by cold bathing. The suggestion of v. Jaksch that an artificial leukocytosis be produced by the injection of turpentine or other irritants which produce abscess, or pilocarpine or nuclein, which do not produce abscess, has been without practical value.

Leukocytosis generally appears soon after the chill, sometimes with it, and probably reaches its maximum within a short time. There may be a slight rise in the number of leukocytes during the period of the decline of temperature. The temperature curve reaches normal before the leukocyte curve. The latter takes from one to three days longer to reach the normal, but may be delayed for some days, even though the lungs are resolving. In delayed resolution the leukocytes remain elevated after the temperature has reached normal and may not fall for some weeks. There is no relative excess of the polynuclear variety. There is no correspondence between the temperature and the leukocyte curve according to Gaitskell. In the majority of cases the leukocytes reach their normal number before the disappearance of abnormal physical signs. In delayed resolution, however, the abnormal signs clear up at about the same time that the leukocytes reach normal. According to Cabot, the polymorphonuclear cells are enormously increased both absolutely and relatively, during the febrile period often making 80 per cent. of the white corpuscles. There is a slight drop in their number during the crisis. On the day after the crisis, there is a further lowering of their percentage. After the leukocyte and temperature curves have reached normal, the polynuclear cells continue to diminish until they are exceeded in number even by the lymphocytes. These latter vary inversely in percentage with the polynuclears. As the polynuclears increase, the lymphocytes diminish in number, and *vice versa*. The large mononuclear and transitional cells follow an irregular course. The eosinophiles are rarely present during the fever. They may appear during the crisis, but more commonly after it. They are present during delayed resolution. They are present in fatal cases, when leukocytosis is wanting, according to Gaitskell. Becker, on the other hand, states that he has never found eosinophiles in fatal cases. According to Cabot, eosinophiles may run up as high as 5 to 6 per cent. after the crisis, but before it they are absent and the lymphocytes are both absolutely and relatively much reduced.

Myelocytes are present during some stage of the disease and may reach 11 per cent. They may precede the crisis or occur during it. They are

found present on the day after the crisis and their numbers are comparatively large after the temperature has fallen. In delayed resolution they are present in small number. They may be present without eosinophiles. The mast cells are rarely unassociated with eosinophiles. They appear during one of the first three days following the crisis. The blood plates are greatly increased after the crisis. Iodophilia is present in practically all cases. Dunn has noticed that it persists in cases of delayed resolution, whereas in normal cases it disappears a day or two after the crisis. According to Bernicot, the absence of iodophilia is a sign of great negative value in cases of suspected delayed resolution or abscess.

The following tabulation shows the high mortality which attends cases with leukopenia:

Observer.	Cases of Pneumonia.	Number without Leukocytosis.	Number Fatal.
Halla	14	2	2
Billings	22	1	1
Laehr	16	1	1
Rieder	26	1	1
Ewing	101	6	6
Cabot	842	90	83
Cabot	49	5	0
Gaitskell	10	2	0
	1080	108	94

Regarding the diagnostic value of the leukocytes Cabot makes the following statements: In central pneumonia marked leukocytosis excludes malaria, typhoid fever, uncomplicated influenza, tuberculosis, and scarlatina if suppuration can be excluded. In capillary bronchitis we find a leukocytosis, so that no inferences can be drawn as to the presence or absence of pneumonia. In the pneumonia of children and the aged a leukocytosis often directs our attention to the lungs. The absence of leukocytosis in pneumonia is a bad sign; its presence does not permit conclusions as to the outcome. The reappearance of eosinophiles is a favorable sign, as is also the disappearance of iodophilia.

The leukocytes were carefully studied in 48 cases of the senior author. In 7 with marked toxæmia the average count was 25,900; 6 of the 7 died. One terminated in abscess, the count reaching 43,800 after the crisis. In 5 cases with moderate toxæmia, the average count was 17,320; 4 of these were fatal. In 36 cases the toxæmia was mild, the average count 23,278, and 3 died. In one of the cases the crisis took place on the seventh day, when the leukocytes numbered 43,000. Leukocytosis does not decrease with a pseudocrisis as it does with the real crisis. If the critical drop of the leukocytes does not occur with a sudden fall of temperature, we are justified in assuming either that the actual crisis has not occurred, a relapse is impending, or complications are present.

Cabot studied the leukocytes in 186 cases with the following results. 24 cases had 10,000 to 15,000, 48 had 15,000 to 20,000, 46 had 20,000 to 25,000, 19 had 25,000 to 30,000, 4 had 30,000 to 35,000, 7 had 35,000 to 40,000, 2 had 45,000 to 50,000 and 4 had 50,000 to 55,000.

The finding of pneumococci in the blood is of no prognostic import, being largely a question of technique.

The subject of cryoscopy of the blood in pneumonia has not as yet been sufficiently investigated to permit of any final conclusions either as to the actual findings or the value of the procedure from a theoretical or practical standpoint.

CLINICAL VARIETIES OF PNEUMONIA.

In addition to the usual type of pneumonia a number of special varieties occur from time to time, which have come to be regarded as more or less definite clinical entities, although some of these are due to organisms other than the pneumococcus and some probably result from mixed infection.

Wandering or Migratory Pneumonia.—Wandering or migratory pneumonia is a form of the disease which tends to spread from one part of the lung to another, resolving in one part while it spreads in another, in much the same way as erysipelas. Of this variety there are two distinct types, one in which the inflammatory process travels by direct continuity or contiguity to neighboring parts, the other in which the disease affects different regions of the same or different lobes as time goes on. The latter variety was called "erratic pneumonia" by Wunderlich, and occurs especially in influenza pneumonia. Fraenkel states that migratory pneumonia is simply an exaggeration of what occurs ordinarily in many typical cases, and maintains that if the latter cases are carefully watched one can often observe small areas giving evidences of resolution, while the consolidation tends to spread in another direction. It is sometimes difficult to draw a distinction between wandering pneumonia and recurring pneumonia, as has been pointed out by Brieger. Homburger, and Ruge have called attention to the tendency of this form of pneumonia to run a protracted course. Migratory pneumonia occurred in 8 out of 813 collected cases (0.98 per cent.).

Asthenic or Senile Pneumonia.—Asthenic or senile pneumonia is a term used to designate the disease as it occurs in senile patients and in those enfeebled by chronic illness or cachexia. It is characterized especially by a gradual insidious onset, often without chill or any prodromal symptoms; in fact in bedridden patients its presence may be unnoticed until it is far advanced, and occasionally it happens that the disease is unexpectedly revealed at autopsy. In other cases we suspect a pneumonia on account of the patient's weakness, respiratory rate, fever, or other symptoms, and yet the most careful physical examination may fail to reveal any definite physical signs until two or three days later. In such case the inflammatory process may begin in the central parts of the lung, and only gradually make its way to the periphery. Charcot refers to lobar pneumonia as "that great enemy of old people, and one of the principal causes of death at the Salpêtrière," and quotes Hourman and Dechambre in speaking of the old women at the above-mentioned hospital: "They do not even complain of malaise; no one in the wards, neither guardians, servants or neighbors, perceives any change in their condition. They get up, make their beds, walk about, eat as usual, then feel a little fatigued, sink upon their beds and expire. The body is opened, and we find a great part of the pulmonary parenchyma in a state of suppuration."

This variety of pneumonia is located often at the apex of the lung. It is frequently accompanied by severe nervous symptoms, such as delirium

and coma. Prostration is nearly always profound. Gastro-intestinal symptoms such as vomiting and diarrhœa may predominate. Cough and expectoration may be absent; dyspnœa is usually not great although the respiratory rate be high, and cardiac weakness is very evident. The temperature may be normal or subnormal and is hardly ever high. The course is a protracted one; when recovery occurs the fever defervesces by lysis and convalescence is slow. Leichtenstern states that complete consolidation of lung tissue is unusual, the stage of red hepatization is short, and the tendency to terminate in abscess or gangrene of the lung quite marked. Certain epidemics of pneumonia have been characterized by the frequent occurrence of this form of the disease, which has been described as "putrid pneumonia," "pythogenic pneumonia" and "typhoid pneumonia." The last term is particularly objectionable, as it suggests typhoid fever, and although pneumonia may occur in typhoid fever or the latter coincidently with the former, and although pneumonia may be caused by the typhoid bacillus, yet these conditions should be sharply differentiated. A large number of asthenic pneumonias end fatally. Œdema of the lungs is a very common complication. As to the actual cause of these asthenic types, Fraenkel states that his investigations permit him positively to deny the suggestion of Leichtenstern, that they are due to mixed infection. He further states that the majority are purely pneumococcal in origin and a few of them purely streptococcal. An increased virulence on the part of the organism, or a decreased resistance on the part of the host, or both would seem to be the most reasonable explanation.

Apical Pneumonia.—Apical pneumonia has long been believed to possess definite clinical features. Thus, delirium and hyperpyrexia are said to be more common. Opinion seems to differ as to the mortality. Apical pneumonia is supposed to be more common in children, and in the aged. Cordell, who has studied this disease in children, finds that it is not rare in early life. The general mortality is the same as in other locations but if uncomplicated in children, this is almost *nil.* Delirium in these cases is not an unfavorable prognostic symptom at any age, is not more common in adults, and there is no proof that it is in the young. Pericarditis is also said to be a more frequent complication in pneumonia of the apices. The right apex is affected about twice as often as the left.

Central Pneumonia.—Central pneumonia is usually simply an incomplete consolidation which has begun in the deeper parts of the lung. This view is held by many authorities and has apparently been substantiated by Lepine, who has studied such cases by means of the *x*-rays. Other observers, such as Packard, hold that "Such an explanation is hardly satisfactory in view of the fact that every symptom of pneumonia may be present without the appearance of physical signs, until possibly late in the course; and they may often be more marked before the appearance of dulness and tubular breathing than after the signs are available for diagnosis."

Closely akin to central pneumonia is the variety which is spoken of as "*latent or larval.*" This occurs in the asthenic forms of the disease, chiefly among the aged and enfeebled, frequently as a terminal infection. As the name implies, the disease manifests itself neither by symptoms nor physical signs but generally some signs could have been elicited if careful examination had been made. Often these cases are discovered only at autopsy. Hourman and Dechambre found 21 latent pneumonias among 49 cases in old peo-

ple, without cardiac or cerebral complications. When such complications do exist, pneumonia nearly always assumes this form. Littlejohn[1] collected 33 cases of latent pneumonia, and called attention to the importance of this variety of the disease from a medico-legal standpoint, sudden death during the third stage being quite common. He found that this type was practically confined to habitual drunkards. The disease is generally far advanced before the patient takes to bed; death often follows sudden exertion but sometimes occurs unexpectedly during the night. Henoch states that latent pneumonia may simulate meningitis.

Terminal Pneumonia.—Terminal pneumonia occurs frequently, especially during the winter months, in patients with debility and chronic disease, such as cardiovascular, renal or pulmonary. There may be little or no elevation of temperature or pulse, and death is often impending before the condition is recognized. Despite the paucity of physical signs, extensive consolidation may be found at autopsy. Among 81 of the autopsies in pneumonia collected by the junior author, 12 were terminal infections.

Abortive Pneumonias.—Abortive pneumonias are those which run their course in a short time, the duration varying from one to three days. They are unusual, and when they occur consolidation has usually been incomplete. Dusch reported 9 such cases among 173, none of them being fatal. The possibility of a "one day pneumonia" is denied by many physicians, but there is much clinical evidence to prove that such a condition does occasionally occur. Bechtold[2] found 10 cases belonging to this catagory among 1,057 cases of pneumonia at the Würtzburg clinic. Chill, high fever and crisis were observed in all of them but the findings on percussion and auscultation differed greatly. The sputum was rusty in only one case, in another traces of bright-red blood were visible. These seemed to be due to a mild hospital infection, all of them occurring close together in one ward.

Postoperative Pneumonia.—Much diversity of opinion exists regarding postoperative pneumonia. In every large hospital from time to time pneumonia occurs among surgical patients shortly after etherization. That anæsthetics and operations may not infrequently be unjustly blamed is shown by such cases as have been reported by Gould and DaCosta, in which unsuspected pneumonia was accidentally discovered just before etherization. A number of theories have been advanced to account for the condition. The possibility of hæmatogenous infection has received considerable attention, but the concensus of opinion seems to be that the infection comes by way of the air passages. Pulmonary infection through the small emboli, hypostatic congestion, infection through the diaphragm, especially in gall-bladder cases, the entrance of infected air into the abdominal cavity when the peritoneum is opened, have all been offered as possible explanations by different observers. The influence of trauma is also important.

Postoperative pneumonia was known before the days of anæsthetics and may follow an operation under local anæsthesia. Just how much the administration of ether has to do with the production of the disease is uncertain. Silk found 13 cases in 5,000 operative anæsthesias, 8 of which occurred in tongue or jaw cases. Von Beck states that owing to the injurious aftereffects upon the respiratory tract the use of ether has been largely restricted at Czerny's clinic. Osler states that there were usually 3 or 4 cases annually

[1] *Edinburgh Medical Journal*, April, 1902.
[2] *Münch med. Woch.*, 1905, vol. lii, No. 44.

at the Johns Hopkins Hospital. Anders found that pneumonia was more common after gynæcological operations than in the general surgical clinics. The greatest number of cases occur in the winter months. Of 95 deaths which occurred in the surgical clinic at Kiel in 1889, Geranulos found that 18 were the results of pneumonia. Postoperative pneumonias are sometimes lobular in character.

Among 1,196 laparotomies at Munich, Gebele found disease of the lung following in 77, or 6.43 per cent. Of these, 53 died—20 from hypostatic congestion, 8 from "ether" pneumonia, 26 from "aspiration" pneumonia, and 14 from embolic pneumonia. Of the latter, 8 occurred with, and 6 without, peritonitis. The right lung was affected in 6, the left in 4, and both in 4 cases. Gebele performed 40 cœliotomies in rabbits, and found that pulmonary emboli occurred in 12 and pneumonia followed in 4. These conditions appeared both in septic and in aseptic operations. It seems, therefore, as if the pneumonia were due to an embolus plus bacteria, which latter may exist in the lung beforehand or be carried there by the embolus.

Among a collected series of 139,101 cases of anæsthesia, pneumonia occurred in 499 (0.35 per cent.). Among 127 autopsies on persons dead from pneumonia, the junior writer found 3 following anæsthesia. The most generally accepted predisposing factors of this variety of pneumonia are: chilling of the patient by evaporation of ether or exposure of the body, retained or aspirated secretions, and direct infection from non-sterilized inhalers. It is probable that several of these causes may be active in a given case; but, as has been stated, the pneumonia may be independent of these and simply coincident. Until we are in possession of more definite knowledge concerning the biology of different strains of the pneumococcus, our explanation of postoperative pneumonia must be based upon suppositions. Czerny suggests that the patients be made to take deep inspirations after the operation, even when painful, as this helps to overcome the tendency to pulmonary hypostasis.

Pneumonia in Childhood.—Leger, in 1823, first pointed out the distinction between bronchitis and pneumonia in children but for many years afterward the last-named condition was confused with collapse of the lungs—atelectasis, which was first described by Joerg, in 1832 and 1835. Nine years later Legendre and Bailly showed that atelectatic lungs could be restored to the normal by inflation, thus proving that the process was essentially different from inflammatory infiltration, which had not previously been realized. In 1851 Barthez and Rilliet established the difference between lobar and lobular pneumonia. The infectious nature of the disease was first suggested by Jürgensen in 1872.

Croupous pneumonia in children often follows a very different course than in adults. A chill may usher in the attack, but quite frequently this is replaced by gastro-intestinal symptoms such as nausea and vomiting, or by nervous derangements, such as convulsions, delirium, drowsiness or stupor. Hence, we may be misled into supposing that we have to deal with typhoid fever or meningitis. Others begin with sore throat, tonsillitis, and erythematous flushing of the skin, thus simulating scarlet fever. Fever is practically always present and frequently high. Careful observation of the manner and frequency of the respirations is of the greatest importance. Movements of the alæ nasi may or may not be present. Among 270 pneumonias in children under 14 years, Schlesinger found 37 lobar, the

rest lobular in type. Holt states that after three years of age all primary pneumonias in children are lobar in character.

E. Levy has reported a case of *congenital pneumonia* in an infant dying forty-nine hours after delivery, whose mother during the latter part of pregnancy had double pneumonia complicated by left-sided empyema. Pneumococci were found in the pus of the empyema and in the lungs of the child. A similar case has been recorded by Netter. A number of investigators have succeeded in producing a transplacental infection in the lower animals. Fox and Lavenson have reported a case of pneumonia in the new-born due to the *Bacillus mucosus capsulatus.*

The duration of the disease is apt to be shorter than in adults, three and five day cases being often seen. The termination by crisis occurs in 68 per cent. of the cases, according to Morse. Pseudocrises are rare but irregularities and remissions not uncommon. The respirations may range from 50 to 80, the pulse from 150 to 170 in infancy. The last-named observer found otitis media in 18 per cent., empyema in 8 per cent., and the prognosis good if the temperature did not exceed 103° F. In infants, nursing becomes difficult, sometimes impossible. Retraction of the diaphragm is often noticeable. Crying as the result of pain is not frequent and when present is suppressed and hoarse. An expiratory grunt coupled with fever is often very suggestive. According to Fraenkel, the heart action is often irregular at, and for some time after, the crisis.

Among 200 cases of pneumonia reported by Pfaunder, 55 were in children. During the first decade the knee-jerks were often absent or diminished, not infrequently before the physical signs appeared. He found this symptom even more constantly present than herpes and believes that it may be of diagnostic use in differentiating pneumonia from meningitis.

This absence of the knee-jerks in pneumonia is sometimes spoken of as Westphal's sign. It was present in 49 per cent. of 65 cases reported by Kephallinos. It occurred in some instances at a time when the diagnosis of pneumonia was still unestablished. In 12 cases in which the date of the return of the reflex was noted it was observed in 6 on the day of the crisis, in 4 on the following, and in 2 on the second following day.

Like adults, children are subject to repeated attacks. In 201 pneumonias in childhood, v. Ziemssen found 14 in the second, 3 in the third and 2 in the fourth attacks. Aufrecht saw a boy who had had three attacks during the first two and one-half years of life, and another boy with two attacks during the first two years. Otitis occurs most often with right-sided pneumonia. It is often impossible to distinguish clinically between lobar and lobular pneumonia in childhood, a fact which is doubtless responsible for the diverse statements which are made. West[1] calls attention to the fact that acute pneumococcal inflammation in children often occurs in a disseminated form. He finds, too, that many cases of bronchopneumonia in children occur without an antecedent bronchitis, beginning and ending just like the acute pneumonia of the adult. However, during life the physical signs show, and in fatal cases the postmortem examination demonstrates, not massive consolidation, but disseminated patches.

Subcutaneous emphysema as a complication sometimes occurs, generally, however, as the result of pertussis and bronchopneumonia. Cotton has

[1] *British Medical Journal,* October 8, 1904.

reported a fatal case, with generalized subcutaneous emphysema in a child aged seven years, accompanied by dyspnœa and cyanosis. Pierson and Carr have reported the same condition in a child aged four years occurring on the thirteenth day of the pneumonia. The emphysema involved the head, neck, trunk, arms, and upper thighs, followed an attack of coughing, lasted three weeks after resolution, and terminated in recovery.

The first sign noted is listlessness and indisposition to play, accompanied by a flushed face. Very suggestive is the disturbance of the respiration-pulse ratio. When this departs from the normal of 1 to 4 (20 to 80 per minute) and approximates 1 to 3 (40 to 120 per minute), expect further indications of pulmonary disease (O'Dwyer). Next to these, Northrup has found the following factors of respective importance: absent or diminished respiratory murmur over one lobe or portion of a lobe; rales of any kind, perhaps appearing only late, either in a localized shower, or diffusely scattered; bronchovesicular breathing—a bronchial whiff; slight dulness, becoming marked only late; and, lastly, cough.

It is well to bear in mind that pneumonia is very common in children, but frequently unsuspected and overlooked. Infants and small children often have no cough, and swallow what expectoration they have. Below the age of four, empyema is frequent. Koplik states that in certain epidemics meningeal symptoms predominate, especially if the apices are involved. The frequency of convulsions at the onset is probably overrated. The infant with pneumonia is apt to persistently refuse food, and to drink with reluctance at long intervals. Various forms of erythema may occur, but herpes, according to Wells, is infrequent. Serious complications are more common than in adults; among these, empyema and otitis media may be especially mentioned.

Termination.—Among 10,159 cases of pneumonia collected by the writers, the disease terminated by crisis in 5,397, or 53.1 per cent. The day of the disease upon which crisis occurred was as follows in 4,718 cases:

Day of Crisis.	Number.	Percentage.
First	1	0.02
Second	27	0.6
Third	183	3.8
Fourth	265	5.5
Fifth	760	15.9
Sixth	681	14.2
Seventh	1,042	21.7
Eighth	629	13.1
Ninth	505	10.5
Tenth	250	5.2
Eleventh	179	3.7
Twelfth	63	1.3
Thirteenth	70	1.4
Fourteenth	17	0.3
Fifteenth	21	0.4
Sixteenth	15	0.3
Seventeenth	10	0.2

Of 5,201 crises, 3,050, or 58.6 per cent. occurred on the odd days and 2,151, or 41.4 per cent., occurred on the even days.

The tendency of crisis to occur on the odd days of the disease, especially the fifth, seventh, ninth and eleventh, was originally pointed out by Traube; but the figures quoted indicate that this tendency is less marked than is

generally supposed. Cases are usually said to end by crisis when the temperature falls from a considerable elevation to normal or below it within thirty-six hours. The average time is generally shorter, from six to twenty-four hours being required for the defervescence. Jürgensen has reported a case in which only four hours were consumed. It is not at all uncommon for the temperature to fall to several degrees below the normal and remain there for several hours or even days. A prolonged subnormal temperature usually indicates systemic exhaustion. Lebert tabulates the duration of the crisis in 110 cases as follows: twelve hours in 45 cases, twenty-four hours in 25 cases, and thirty-six hours in 40 cases.

The figures given by different writers vary from 15 to 49 per cent. as occurring in twelve hours or less, from 21 to 37 per cent. between twelve and twenty-four hours, and from 8 to 29 per cent. between twenty-four and thirty-six hours. Grisolle found in 192 cases that the physical signs of beginning resolution antedated the crisis in 72, followed the crisis in 72, and occurred simultaneously in 92.

Crisis is more apt to occur in children than in adults, in adults than in the aged, and in brief than in protracted cases. Lysis, on the other hand, is seen more frequently in the aged and in those enfeebled by acute or chronic disease. Among 8,667 collected cases, 2,161 (24.9 per cent.) terminated by lysis. Such an ending of the disease also occurs in atypical varieties, such as are due to other organisms than the pneumococcus, or those in which there is mixed infection. There seems to be a tendency at certain times in different epidemics for pneumonia to terminate preponderatingly by crisis or by lysis, a fact which was pointed out by Wagner. Cases defervescing by lysis should always make us consider the existence of complications.

A number of fanciful explanations have from time to time been offered to account for the occurrence of the crisis at certain times. Thus, Brunner has prepared some elaborate tables which he believes demonstrate the fact that the course of croupous pneumonia bears certain definite relations to the phases of the moon. He considers that the crisis is influenced by certain cosmic causes, perhaps through periodic variations in gravity. As to the hour at which crisis is most apt to occur, Wunderlich is responsible for the statement generally quoted that this is in the late evening hours, sometimes in the afternoon or at night and rarely in the forenoon or at midday.

The crisis is often accompanied by extreme exhaustion and relaxation, a condition which is manifested by sweating, a rapid, weak, irregular pulse of very low tension, frequently dicrotism, epistaxis, profound sleep, polyuria, diarrhœa, and occasionally incontinence of urine. Sweating occurred in 9 out of 43 cases. Crisis occurring as late as the nineteenth day of the disease has been reported.

Pseudocrisis consists in a rapid fall of the temperature which closely simulates the termination of the disease, but which is followed in the course of a few hours by a subsequent rise of the fever to, or even above, its original height. In favorable cases the pseudocrisis is followed in the course of a day or two by the true crisis. Among 54 pseudocrises collected from 500 cases at the Pennsylvania Hospital, Philadelphia, the following distribution was noted:

Day of Crisis.	Number.	Percentage.
Second	1	1.9
Third	2	3.7
Fourth	2	3.7
Fifth	2	3.7
Sixth	12	22.2
Seventh	11	20.4
Eighth	6	11.1
Ninth	1	1.9
Tenth	5	9.3
Eleventh	1	1.9
Twelfth	2	3.7
Thirteenth	1	1.9
Fourteenth	2	3.7
Fifteenth	2	3.7
Sixteenth	2	3.7
Seventeenth	1	1.9
Eighteenth	1	1.9

Of the foregoing cases, 2 had two pseudocrises, one upon the third and the seventh, the other upon the third and the eighth days. There were only 5 fatal cases among these 54, a mortality of 9.2 per cent., as contrasted with a general death-rate of 25 per cent. Among collected cases, 172 in 1,854 had pseudocrises (9.8 per cent.).

Duration.—The duration of lobar pneumonia ranges from one day to three weeks. Naturally the majority of the cases are not to be classed at either end of this limit; most of them last from five to ten days. In children three- and five-day pneumonias are by no means rare; and no less an authority than Aufrecht believes than even in adults "one-, two- or three-day pneumonia" is commoner than generally supposed. Leube has reported 2 cases of pneumonia lasting one day; Thomas, 3 cases of two-day duration, and Tophoff, Baruch and Bernhard, similar cases. The senior author has seen 1 case of two-day pneumonia with all the characteristic symptoms and signs; the bronchial breathing lasted four days after the crisis. Aufrecht states that "many a status febrilis, many a febris ephemera, whose cause cannot easily be found may etiologically belong to this group of pneumonias." Broadbent has reported a case with abortive crisis and premature resolution in forty-eight hours, in which the symptoms of toxæmia were severe.

In contradistinction to brief or abortive pneumonia we have *delayed resolution*, migratory and recurrent pneumonias. The first-named condition is met with chiefly in old and debilitated subjects. Cimbali states that it bespeaks a subnormal resistance on the part of the patient, and occurs with especial frequency in malarial cachexia and in cases in which there is cardiac weakness; he has never seen a relapse follow this condition. It must always be borne in mind that delayed resolution may be very closely simulated by tuberculous pneumonia, by chronic apical infiltration, by interlobar empyema or pleural effusion. Delayed resolution was reported in 105 among 2,548 cases (4.1 per cent.). Under normal conditions resolution is accomplished through a process of autolysis, the metabolic changes being very closely allied to those which occur during the digestion of proteids.

Flexner has shown that the intensity of the autolytic power varies in the different stages of the disease, the highest activity being encountered durnig the stage of gray, and the lowest in the stage of red, hepatization, a condition which is perhaps due to the larger number of leukocytes present in the former. In unresolved pneumonia both autolytic power and leuko-

cytes are low. Flexner attributes the failure of the exudate to be absorbed to the disproportion between leukocytes and other constituents. Opie has shown that failure of autolysis is, at least in a measure, due to the presence in the blood serum of an antilytic substance.

In favorable cases the lung eventually clears up, absorption of the exudate being slowly accomplished; in others restitution does not occur at all and the exudate gradually undergoes fibroid induration, or suppuration.

Andral was the first to describe *termination in fibroid induration* in unequivocal terms. Stokes described a case followed by marked retraction of the chest wall, empyema having been definitely excluded. Clinically delayed resolution is apt to be confused with old tuberculous lesions, secondary tuberculous infections, and tuberculous pneumonias, from all of which they are entirely distinct. Fraenkel, who has carefully studied some 12 cases, found that in every instance there were evidences of connective tissue formation in the alveolar exudate. He states that in every case in which resolution is delayed beyond three weeks without definite cause—complications, such as abscess formation, etc.,—we must assume that fibroid induration has begun. Macroscopically two varieties, the red and the gray, as originally described by Andral, are to be noted, having more or less the appearance of polished granite, the reddish hue being due either to the vascular richness of the tissue or to newly formed capillaries. Later the color fades to grayish-yellow, as the result of fatty degeneration of the alveolar tissue. Months later the involved areas become pale gray, indurated, shrivelled, and of a tough consistence.

In delayed resolution there is continued fever, gradually subsiding in favorable cases. In drunkards and cachectic individuals a fatal termination is not infrequent. In this class the fever increases, becomes more irregular, and not infrequently leads one to suspect that the disease may have been a tuberculous pneumonia from the onset. Death may occur suddenly but usually ensues as the result of gradual heart failure, the fatal termination being frequently preceded by delirium, coma, etc. In some cases, as was pointed out by Wagner, the percussion dulness, bronchial breathing and rales may gradually disappear, as the result of a compensatory emphysema of the surrounding tissue, and by the resumption at least in part of activity by the infiltrated area. According to Charcot these cases do not develop bronchiectasis; however this may be, it seems that a fibroid induration of the lung does predispose to other pathological changes, notably gangrene. These cases may be closely simulated by serofibrinous or purulent pleural exudates, interlobar empyema and abscess of the lung. Exploratory puncture, careful microscopic examination of the sputum and the leukocyte count, will often help in the solution of the problem. The absence of fever is strong evidence against the presence of abscess or empyema.

Relapse.—Much misunderstanding exists on the subject of relapse, partly from its inherent difficulty, and partly from the multiplicity of terms which have been employed by different authors. Thus, we find that confusion is caused by the failure on the part of some writers to distinguish between pseudocrisis, migratory infection, relapse and recurrence. Then, too, the question often arises as to when a condition should be regarded as a relapse, and when merely as a pseudocrisis. Ebstein suggests that the diverse nomenclature be dropped and that the terms, "early recurrence" and "late recurrence" be substituted. Relapse should be spoken of only

when a fall in temperature is followed after a time (two to three days) by undoubted evidences of beginning resolution, whereupon a fresh attack is subsequently precipitated, which invades the same location as the original one. In this way we distinguish the condition from migratory pneumonia in which new areas are involved. Wagner has given the following definition: "If the lung, after an ordinary croupous pneumonia involving one or several lobes, becomes normal after the fever has terminated by crisis or lysis, the patient is convalescent; and if at least three days to several weeks after the defervescence a new infiltration of the same or other lobes with all the characteristic phenomena of a local and general nature occur, a relapse has without question taken place."

Relapse in pneumonia is rare. Osler states that he has seen but 2 cases. Among statistics, 36 instances occurred in 5,966 pneumonias (0.60 per cent.). Chatard found 5 in 658 pneumonias. Fraenkel encountered 7 relapses in 1,000 cases as follows:

No.	Duration of First Attack.	Interval.	Duration of Second Attack.
I	11 days	16 days	3 days
II	6 "	1 day	10 "
III	5 "	26 days	5 "
IV	12 "	11 "	12 "
V	3 "	3 "	2 "
VI	7 "	5 "	3 "
VII	6 "	3 "	5 "

In 5 of these cases the signs of the primary consolidation were still present at the onset of the second attack. The first 6 of the cases occurred between April and November, 1892. Ruge has reported 7 cases of relapse in which there was an afebrile period lasting from four to fifteen days, during which there was an apparent convalescence with partial disappearance of the physical signs; the duration of the relapses was from four to eight days.

More than one relapse may occur; Grisolle saw 3 attacks in the same individual within twenty-seven days. It is hardly probable, however, that resolution, in this case, could have advanced very far between the attacks; it may have been an instance of pneumonia migrans. The duration of a relapse is usually short. Second attacks occurring after a long period of time must of course be considered as recurrent infections. Sometimes there is a tendency for the disease to recur in the same portions of the lung.

Death.—Death in pneumonia usually comes on gradually with the signs of cardiac failure. The pulse progressively weakens, finally becoming irregular and intermittent. The respirations grow more superficial and ineffectual. The cough subsides and the sputum is no longer expectorated but blocks the bronchial tubes. The extremities become cold. Cyanosis is replaced by an ashen-gray pallor; and, finally, pulse and respiration cease. Sometimes during the last few labored respiratory efforts the patient starts up convulsively and takes a last conscious glance at his surroundings but, as a rule, death comes on insidiously. The stage of dying, as a rule, lasts several hours but at times the end comes suddenly and unexpectedly, as the result of cardiac or pulmonary thrombosis. If death be due to severe toxæmia, there may be few signs of circulatory failure until near the end.

Sudden death generally occurs during the stage of gray hepatization, and in such cases often neither the seat nor extent of involvement, nor the

apparent gravity of the case seem to bear any constant relation. It is usually precipitated by sudden exertion. Sudden death in children has been reported by Terrien, Leroux and others. In the latter's case, a girl aged five years, who had a pneumonia of the right apex, following tonsillitis, accompanied by hyperpyrexia, died suddenly without warning on the third day of the disease.

The following tabulation shows the *day of the disease* upon which *death* occurred in 2,613 collected cases.

Day of Death.	Number.	Per Cent.
First	6	0.23
Second	60	2.30
Third	95	3.64
Fourth	124	4.75
Fifth	189	7.23
Sixth	209	8.00
Seventh	230	8.80
Eighth	225	8.61
Ninth	206	7.88
Tenth	175	6.70
Eleventh	125	4.78
Twelfth	93	3.56
Thirteenth	60	2.30
Fourteenth	82	3.14
Fifteenth	53	2.03
Sixteenth	41	1.57
Seventeenth	41	1.57
Eighteenth	33	1.26
Nineteenth	37	1.42
Twentieth	25	0.96
Twenty-first	59	2.26
Later	445	17.03

Pneumonia may terminate in a general *pneumococcus septicæmia*, or by metastatic suppurative foci in practically any part of the body. Such infection may be carried either by the lymphatics or the blood stream. According to Bloch, who studied 30 cases, the former route is the more common, the latter indicating a special predisposition such as is afforded by debility from recent infectious disease, by the rapid growth of the young, or by a congenital tendency. Pneumococcic infection in various organs or tissues may of course occur without a preceding pneumonia. In such cases it may be impossible even at autopsy to determine the origin of the infection.

In cases of general or localized pneumococcus infection without the occurrence of a preceding pneumonia, we quite commonly find four cardinal symptoms present which are very suggestive of the condition· namely: chill, sudden pyrexia, leukocytosis and herpes. One or more of these symptoms may occur in a variety of other morbid processes, but the simultaneous appearance of all of them in a given case should make us very strongly suspect the pneumococcus as the etiological factor. Definite information may be obtained from blood cultures, lumbar puncture, etc. Pneumococcus septicæmia, secondary to local infection, has been reported by many writers. A further consideration of this subject will be found in the section on complications.

Experimentally it is very rarely possible to produce a pneumonia by inoculation with the pneumococcus, even when the animals are exposed to cold or when other artificial means are adopted. Wadsworth has, however, found

that when animals are first partially immunized against the pneumococcus, and their resistance raised instead of lowered, intratracheal injections of pneumococci give rise, in a large proportion of cases, to extensive lobular pneumonia or to true lobar pneumonia. He believes that by this process of partial immunization the rabbit is brought nearer to the condition of man, who possesses a certain degree of resistance to infection by this organism. Thus, in man, after infection by the pneumococcus, in place of a rapidly fatal septicæmia, the lungs sustain the brunt of the assault and in this situation there is set up a localized inflammation. But this process is not entirely local. In the majority if not in all cases pneumococci gain entrance into the blood and produce a systemic infection. Rosenow has grown the pneumococcus from the circulating blood in 91 per cent. of 175 cases.

THE PHYSICAL SIGNS OF LOBAR PNEUMONIA.

But little information of practical value can as a rule be obtained by *mensuration* of the chest in pneumonia. Broussais claimed an enlargement of the diseased side, but Andral, Laennec and Woillez did not substantiate this. Certainly the data obtained by this method are not commensurate with the time required, or with the discomfiture given to the patient. Diminished excursion of the diaphragm or of the chest is often observed on inspection. If the pain is severe, inspiratory expansion may be limited. Immobilization of the affected side does not occur to the same extent as it does in cases of pleural effusion. Compensatory excursions on the healthy side may occur, as well as abnormally increased action on the part of the accessory muscles of respiration.

Percussion and *auscultation* give most important data. During the early congestive stage a hollow tympanitic note is often encountered. According to Aufrecht this is due to the swelling of the alveolar epithelium from overdistended capillaries and "as a result of this the elasticity of the pulmonary structure is lessened and under percussion the pulmonary area does not vibrate as in the normal lung. The tympanitic note is the result of the loss of elasticity of the pulmonary structure due to anatomical reasons; the amount of air in the alveoli is no longer enclosed in so markedly stretched membranes as in the normal state." As consolidation begins, dulness replaces the tympany, although as Thomas has pointed out, a tympanitic quality may remain, this being especially noted when the apices are involved, in which case as the result of imperfect consolidation in the early stages, tympany is more marked, and later, dulness is less intense.

In the early stage of a central pneumonia there may be hyperresonance of the entire chest, at times to such an extent as to make the sound side seem relatively dull, and hence a mistake may be made as to the side affected. In cases of central pneumonia the resonance may never become more than "impaired." Another explanation places the origin of the tympany in the vibration of the air within the bronchi which are surrounded by consolidation, as the result of which the percussion impact is transmitted with greater intensity to the bronchus, and the vibrations are in turn conducted back with more distinctness. Jürgensen mentions two cases in which percussion of the completely solidified lower lobes produced typical tympany, the pitch changing when the mouth was opened and closed. Sometimes when the

lower lobes are involved tympany may result from the proximity of the stomach. Hyperresonance often occurs as the result of compensatory action on the part of the healthy lung tissue; in some cases it covers a neighboring lobe to that which is diseased; in others the entire opposite side of the chest is involved, this being largely dependent upon the extent of the consolidation. A cracked-pot sound may occasionally be elicited, when infiltration surrounds a large bronchus. Aufrecht explains this as due to the unequal effect of percussion at the border between the edge of the consolidated and the healthy lung tissue, considering the phenomenon as due to sound wave interference. The area of dulness tends to be somewhat larger than the consolidated area. Associated with the dulness there is a distinct sense of resistance felt by the percussing fingers, which is sometimes more striking than the actual change in resonance.

In extensive consolidation, dulness may almost reach the degree of flatness, although the latter condition is always suggestive of pleural exudate, either plastic or liquid. When the upper lobes are first involved, dulness quite frequently first appears in the posterior axillary line, and if at a high level, it may be overlooked. In all cases in which pneumonia is suspected and cannot be definitely made out, the upper axilla should be very carefully percussed and auscultated. Wintrich states that "pulmonary tissue devoid of air and peripherally infiltrated gives a short weak note on percussion, only if the space devoid of air has a diameter of about five centimeters and a depth of two centimeters, and then only upon superficial percussion." For this reason small areas of involvement may be difficult to determine. In each case, therefore, both light and heavy percussion should be practiced, the former for superficially, the latter for deeply, situated lesions.

Associated with the *crepitant rale* in the early stages, we generally have more or less suppression of the vesicular murmur, later vesiculo-bronchial, broncho-vesicular, finally bronchial and tubular breathing. When true tubular breathing exists crepitant rales disappear. Suppression of the vesicular murmur is very common, and often the condition persists over the greater part of the consolidated area throughout the attack, especially in asthenic cases. This is the result of incomplete, diffuse infiltration or obstruction of the small bronchi through excessive secretion. The fact that tubular breathing may be absent is often very puzzling to the young practitioner who has acquired the idea that in all cases of pneumonia loud tubular breath sounds are to be heard. One not infrequently has to make a diagnosis of pneumonia on slight percussion dulness, suppressed vesicular murmur, a few subcrepitant rales, fever and increased respiratory rate. In typical sthenic cases, however, the breath sounds going through the stages mentioned, finally become loud, and typically tubular in character. Tubular breathing may be heard during both inspiration and expiration; its intensity depends largely upon the completeness of the consolidation. It gives one the impression of sounds produced very close to the ear.

The statement made by Laennec that the crepitant rale is the most characteristic sign of pneumonia still holds good, although of course it is not pathognomonic. It is heard during inspiration, chiefly during the latter half, and consists of showers of fine, high-pitched, resonating sounds which have been aptly compared to the crepitation produced by the rubbing of a lock of hair held close to the ear, to the crackling of a static electric machine with the poles closely approximated, or the sound produced when salt is thrown

upon a fire. Crepitant rales are produced by the inspired air breaking through small collections of tough secretion at the point at which a terminal bronchiole merges into an alveolus. They must not be confounded with subcrepitant rales which are heard in œdema of the lungs, hypostatic congestion, and catarrh of the finest bronchioles. They differ from the latter in that the sounds are finer, higher-pitched, more ringing, metallic and dryer in character. Although crepitant rales are generally classified as moist rales they possess some of the qualities of the dry variety. The crepitant rale is produced in the lung only when the above described conditions of localization of secretion are accompanied by some consolidation, as in early pneumonia, tuberculosis, hemorrhagic infarct or atelectasis. It may, however, be very closely simulated by the subcrepitant rale and by a fine pleural friction. The crepitant rale is one of the earliest signs of pneumonia; it may be only intermittently present for obvious reasons, and disappears entirely when consolidation becomes complete, to return later on as "crepitus redux" when resolution begins, at which time, however, it is often replaced by subcrepitant rales. It is heard only over the pneumonic area.

In cases with marked consolidation and bronchial breathing, uncomplicated by pleural effusion, loud high-pitched *bronchophony* occurs, which according to Laennec, results from abnormally intense conduction through the solidified lung tissue. Skoda explained it as being due to the consonance of the air in bronchial tubes surrounded by infiltration. According to Aufrecht it is caused by the presence of quiescent columns of air in the bronchi, such columns alone being capable of transmitting the vibrations of the vocal cords to the pulmonary tissue. Bronchophony occurs only when consolidation is complete. It is more common in men than in women, owing to the fact that the former speak from the chest. At the end of a spoken syllable, a short, harsh, rough expiratory puff is heard, which the last-named author explains as "very likely due to the more passive expiratory collapse of the thoracic wall."

Associated with bronchophony, due to the same causes and subject to the same exceptions, we find increased *vocal fremitus*. This generally allows us to exclude the presence of pleural effusion but its absence permits of no positive deductions. It may be temporarily absent owing to excessive bronchial secretion; in such cases cough may cause its re-appearance. In some cases it is persistently diminished or even absent. Gerhardt states that in cases with intense consolidation, such as those in which at autopsy the outlines of the ribs are furrowed upon the periphery of the lung, fremitus is absent. Thickened pleura may cause similar results. Much less weight can be attached to the condition of the vocal fremitus than to the findings of auscultation and percussion.

Graves called attention to the fact that disseminated beating synchronous with the heart's action may be noted in the early stage of pneumonia; and likens the condition to a half-filled sack of fluid. Skoda described a pulsation of the hepatized area, not infrequently synchronous with the heart, a condition probably due to arterial pulsation in the engorged lung.

Conner and Dodge[1] carefully studied 392 cases of pneumonia in the early stages, with the intention of learning the relative importance of the various physical signs. Their findings are tabulated in the order of importance as follows:

[1] *American Journal of the Medical Sciences*, September, 1903.

1. Circumscribed area of feeble and indistinct breathing compared with the opposite side.
2. Circumscribed impairment without or with a tympanitic quality (sitting up).
3. Crepitant rales.
4. Slight increase in intensity and clearness of vocal resonance.

Benczur and Jonas have made quite elaborate claims for the advantages of *thermopalpation*, a procedure by which they believe it is possible to locate the seat of the pulmonary inflammation by an increase in the temperature of the overlying skin, perceptible to the touch. They state that they have demonstrated by the thermometer that such temperature changes do occur. Meisner was unable to substantiate these findings. Aufrecht inclines to the belief that thermopalpation has some value in cases in which percussion is unavailable, such as fractured ribs, hæmoptysis or aneurism; although it does not yield any data which cannot be obtained by other means. In order to carry out this test the patient's chest must be uncovered for a short time before the attempt at temperature differentiation is made, as the effect of bedclothes is to make the heat of the skin more evenly distributed.

Occasionally we find abnormal physical signs on the sound side of the chest. Thus when consolidation exists at the root of one lung, we may have a transmission of bronchial breathing to the opposite side. Not infrequently we find some dulness and rales on the sound side, without there being any actual consolidation. This arises from the fact that one lung being in part consolidated, there is a tendency for more blood to pass through the sound lung; and if there is any weakness of the right heart it is apt to stagnate there; in addition, the vicarious breathing on the sound side produces more negative pressure, so that blood flows in more freely from the pulmonary artery.

THE COMPLICATIONS OF LOBAR PNEUMONIA.

The true *complications* of pneumonia are really expressions of the pneumococcus infection in other organs and tissues than in the lungs. The following tables arranged in order of their frequency, show the results of collected cases:

Clinical Observations.

Complications.	Total Cases.	Number With.	Percentage.
Albuminuria	4,792	2,184	45.58
Pleural effusion	24,511	1,535	6.26
Chronic nephritis	7,080	193	2.73
Empyema	13,550	303	2.2
Jaundice	22,544	373	1.65
Pulmonary tuberculosis	19,638	343	1.7
Acute pericarditis	40,773	499	1.2
Acute nephritis	30,042	367	1.22
Phlebitis	2,360	17	0.72
Abscess of lung	12,030	76	0.63
Cirrhosis of liver	3,644	19	0.52
Acute arthritis	28,645	150	0.50
Gangrene of lung	27,761	136	0.49
Acute tonsillitis	4,052	16	0.46
Acute endocarditis	32,349	144	0.44
Acute meningitis	49,028	206	0.42
Acute parotitis	2,655	10	0.37
Acute peritonitis	8,132	28	0.34
Pregnancy	13,611	120	0.8

Autopsy Records.

Complications.	Total Cases.	Number With.	Percentage.
Pleural effusion	974	405	41.58
Nephritis (acute)	7,020	1,334	19.00
Nephritis (chronic)	2,218	573	25.83
Acute pericarditis	2,128	267	12.6
Otitis media	54	4	7.41
Acute endocarditis	2,693	157	5.8
Gangrene of lung	1,914	100	5.2
Empyema	973	50	5.1
Acute meningitis	4,833	180	3.5
Abscess of lung	1,294	28	2.1
Acute peritonitis	971	21	2.1
Acute arthritis	698	4	0.58
Pulmonary thrombosis	1,830	5	0.27
Acute hepatitis	293	155	52.9

Pleurisy.—Among the complications which may arise in the lung itself, we may begin with the commonest—*pleurisy*. When we consult the histories of pneumonia cases we find that often this complication has been left unrecorded. By reason of its great frequency it is often unmentioned in the clinical notes, unless it was of marked severity or was accompanied by effusion. Hence the recorded data would make the condition seem much less common than is really the case. Pleuritis occurs in practically all the cases, or at least in those cases in which the inflammatory process reaches the surface of the lung. It usually corresponds to the location of the pneumonia, although occasionally it may be met with on the opposite side. It is recognized by the well-known symptoms and signs—pain, restriction of motion and a friction rub on auscultation. The latter symptom may be transient and often difficult to differentiate from intrapulmonary rales. These so-called dry pleurisies are often accompanied by a plastic exudate, which later on may give rise to adhesions, and thickening of the serous membrane.

Small liquid effusions are apt to be overlooked during the active stage of the disease and to become apparent only after resolution has begun. Maragliano by using the exploring needle was able to demonstrate sero-fibrinous, or fibrino-purulent exudate in 38 out of 58 cases (65.5 per cent.). According to Preble the adult pleura must contain 400 cc. of liquid before its presence can be demonstrated by physical signs. In 127 autopsies in pneumonia, the junior author found pleuritis 59 times (46.4 per cent.), as follows: fibrinous 23, serous 5, fibrous 11, purulent 20. In 173 pneumonia autopsies, Kerr found 74 cases of acute fibrinous, 38 cases of acute sero-fibrinous, and 6 of acute purulent pleuritis. The effusion may occur at any time but seems to be most common on the fourth or fifth day. Among Sello's cases it was found at the beginning of the attack in 2, during the attack in 31, and afterward in 24 cases. The largest amount of effusion recorded was 600 cc. Large, rapidly increasing, serous effusions may occur and seriously embarrass respiration and the heart. Of 33 cases, 28 were negative bacteriologically and 5 positive, 3 showing pneumococci.

Among 24,511 collected cases, 1,535 had *pleural effusion* (6.26 per cent.). Of 700 such, 142 or 20.29 per cent. died. Of 949 autopsies, 405 or 41.58 per cent. had effusion. It would seem therefore that the presence of effusion does not materially influence the prognosis but of course very large exudates might readily do so. This may have been the case among Fismer's material, he having found that the mortality was doubled by the complication.

Among 27 cases of complicating pleural effusion, Hadden, Mackenzie and Ord found that in 14 the exudate was on the opposite side to that on which the pneumonia existed.

The diagnosis is to be based upon the usual signs of pleural effusion but it must be borne in mind that the exudate may be loculated. Doubtful cases should be definitely determined by the use of the aspirating needle, as there is always the possibility that the effusion may be purulent in character.

Laryngitis and Bronchitis.—Laryngitis and bronchitis may precede or complicate pneumonia. Bronchitis is practically always present, and it is often difficult to say at what point a bronchitis should be considered a complication or merely a part of the disease, it being largely a question of degree and of distribution. Recent bacteriological research has shown that acute infections of the respiratory tract may be caused by the pneumococcus. It is probable that such infections under favorable conditions directly lead to an attack of pneumonia. A complicating bronchitis or laryngitis may therefore really be the initial infection. Laryngitis is much less frequent, and may be a serious complication, as in a case reported by Thornton in which an œdematous condition necessitated a tracheotomy at the onset of the disease, but in which recovery eventually occurred. A similar case has been reported by Dorange. In 2 cases seen by Landgraf, laryngoscopical examination, prompted by aphonia, disclosed marked congestion of both the true and the false cords, with deep ulceration which healed slowly.

Empyema.—Empyema occurred clinically among 13,550 collected cases in 2.2 per cent., and at autopsy was found in 5.1 per cent. of 973. As Preble points out, it is curious that the pneumococcus, which in the lungs only rarely produces suppuration, does so with great frequency when it attacks the serous membranes. Among 325 consecutive cases of empyema at Guys Hospital in London, Hale White[1] found that 12.6 per cent. followed pneumonia. In one case 170 ounces of pus were found, in another 100 ounces were secreted within twenty-four hours. Of the 45 cases, 13 died, a mortality of 29 per cent. White's investigations, which include 1,341 cases of pneumonia, occurring between 1883 and 1898, seem to indicate that the frequency of empyema as a complication is increasing. Among his 45 cases of empyema, pyopericardium occurred once, pneumococcus endocarditis three times, arthritis once. In 288 cases of empyema in children at the Mt. Sinai Hospital, New York, pneumonia was the etiological factor in 182. Ewart has called attention to the fact that in children 75 per cent. of all empyemas owe their origin to the pneumococcus and 25 per cent. to the *Streptococcus pyogenes*, but that in adults this state of affairs is reversed. Empyema generally occurs during the stage of resolution. Pneumonia complicated by empyema rarely terminates by crisis. Sello found only 1 among 30 which did so.

In 500 cases of pleuritis collected from the records of the Pennsylvania Hospital, Philadelphia, by F. Fraley, there were 95 cases of empyema. Of these 48 gave a history of having had previously one attack of croupous pneumonia, 3 had had two attacks, and 2, three attacks. Of these 95 empyemas, 35 immediately followed croupous pneumonia. Among 75 empyemas, only 21 had a definitely hectic type of temperature, and 5 of them—chronic cases—were entirely afebrile, the pus in several of which

[1] *Lancet*, November 10, 1900.

proved sterile. Three cases of unilateral empyema, following bilateral pneumonia, recovered after operation. The occurrence in relation to age was as follows: under five years, 11; five to ten years, 8; ten to fifteen years, 9; fifteen to twenty years, 15; twenty to thirty years, 27; thirty to forty years, 12; forty to fifty years, 6; fifty to sixty years, 6, and sixty to seventy years, 1.

Pneumothorax was noted 4 times in 95 empyemas and 4 times in 405 cases of non-purulent pleuritis. Abscess of the lung followed empyema 4 times. Twenty-one out of 95 died (22 per cent.). The following terminations were encountered: 1 ruptured through the diaphragm—peritonitis, 2 ruptured into the lung, with evacuation through the bronchus, and 1 ruptured externally.

In 46 out of 95 empyemas the following organisms were found: in 1, tubercle bacilli; in 24, pneumococci; in 10, streptococci, and 11 were sterile. Pyopneumothorax was found 4 times, one of these being due to pneumonia. In 268 cases, Netter found that 215 were under thirty years of age; among Sello's cases, 15 were under thirty years, 27 under forty years of age.

The symptoms of metapneumonic empyema consist of fever, continuous with or coming on after that due to the pulmonary inflammation. Chills may occur, but generally do not, except at the onset of the fever, which often rises rapidly to a considerable degree. Sweats are of frequent occurrence, especially at night, but pain and dyspnœa are rarely noted. Leukocytosis is generally found and is very suggestive, especially if it reappears after a post-critical absence. The physical signs are those of pleural effusion and need not be dwelt upon, save to say that the exploring needle should be unhesitatingly and repeatedly used in doubtful cases, for when the exudate is encysted or between the lobes, a positive diagnosis may be impossible without this procedure.

The exudate of a pneumococcus empyema is odorless, thick, greenish-yellow, and rich in cellular elements. Microscopically the leukocytes are mostly of the polymorphonuclear variety, mononuclears and endothelial cells being relatively few in number. Generally the pneumococcus is found; sometimes there is a mixed infection with pyogenic cocci, such cases being more severe in character and accompanied by a higher mortality. Sometimes spontaneous absorption may occur but such an event should never be expected or awaited. Occasionally aspiration may bring about a cure, but generally resection of the ribs is necessary. If let alone, the pus may rupture into neighboring structures such as the lung, bronchus or pericardium. External rupture through the intercostal spaces has occurred, but is of great rarity. Œdema of the overlying skin is very infrequent.

Netter states that metapneumonic empyema ruptures into the bronchus in about one-fourth of the cases. When spontaneous evacuation occurs, it generally does so during the third or fourth week, rarely before the third or after the sixth. Such an event may be suspected if there is a sudden expectoration of large amounts of purulent matter, and a lessening of the intensity of the physical signs, of the temperature or of the general constitutional symptoms. The operative mortality in this class of cases is low, lower in fact than in other forms of empyema, ranging from 2 to 5 per cent.

Pneumothorax.—Among the very rare complications of pneumonia, pneumothorax should be mentioned. This is most frequently met with in cases of empyema, as the result of the latter rupturing into the bronchus or

lung. Fismer found 2 such cases among 230 pneumonias. Empyema is not however a necessary factor. In an analysis of 51 cases of pneumothorax, Morse found 3 in cases of pneumonia complicated by abscess, and one by gangrene of the lung. In none of the abscess cases were there any symptoms at the time of onset. The physical signs were discovered on the seventh, fourteenth and twenty-sixth days respectively, after the onset of the pneumonia. In all of them the pneumothorax was open, and purulent. One was not operated upon, and died on the fourth day after the discovery of the pneumothorax. Those operated on recovered. The patient with gangrene died; operation was not done.

Hydropneumothorax.—Hydropneumothorax in pneumonia has been reported by Anthony, coming on on the fifth day, with absence of breath sounds, dulness and amphoric breathing in the central regions, and succussion splash. Displacement of the heart necessitated thoracentesis; 1,100 cc. of sero-fibrinous exudate were withdrawn, in which pneumococci were found in pure culture. The subsequent empyema was treated by resection of the ribs; death occurred three months later.

Abscess of the Lung.—Abscess of the lung occurred clinically in 76 among 12,030 cases (0.63 per cent) and at autopsy was found in 28 of 1,294 cases (2.1 per cent.), a frequency which can by no means be ignored. At the Pennsylvania Hospital, Philadelphia, Fraley found 4 cases of pulmonary abscess among 500 cases of pleuritis. Two followed pneumonia; in the remainder no definite cause could be established, although pneumonia was suspected as both were associated with empyema. Holt states that in 7 per cent. of the autopsies upon infants and young children dying of pneumonia, abscesses are found. They are usually small and, as a rule, multiple; they are rarely clinical conditions. Among several hundred pneumonia autopsies Laennec had found only "five or six cases," most of them having been small in size. Andral found but one case which occurred in the middle and lower lobes, during the stage of gray hepatization. The pus was non-odorous, contained in the centre a dirty grayish mass, and was surrounded by soft and boggy lung tissue. In the past, abscess of the lung and empyema have been frequently confused and reasonably enough, for the symptoms of the two conditions may be similar, especially if the former is situated near the surface of the lung. Among 750 cases of pneumonia, Sello found abscess in 11, 9 being males and 2 females; 4 were fatal and 5 were associated with empyema Some occurred early in the course, one on the seventh, and one on the eleventh day.

Grisolle's study based upon 29 cases, shows that abscesses are generally found near to the surface, measure from 3 to 5 cm., have an irregular sinuous outline, their walls being bounded by shreds and tissue detritus. In rare cases a limiting membrane is found. Abscesses vary in size, may rupture into the pleura and have been known to empty themselves into the pericardium. Such cases have been reported by Beclard, Grisolle and others. In the cases of the last-mentioned author the age distribution was as follows: fourteen years, 1; sixteen to twenty-six years, 4; thirty-one to thirty-six years, 5; forty-five to forty-nine years, 3; fifty to fifty-nine years, 4; and sixty to seventy years, 8 cases. Eleven of these were on the right side and 16 on the left. Rupture into the œsophagus has occurred.

Pulmonary abscess usually develops insidiously, producing no symptoms which are characteristic at first. The sputum is increased in amount and

yellow in color, later becoming greenish. At times it may contain blood pigment, or assume a green or blue color by virtue of different chromogenic microörganisms. When the abscess is large the quantity of purulent expectoration may amount to several hundred cubic centimeters daily. In the later stages it is sometimes offensive. Both cough and expectoration often vary greatly with the position of the patient. Microscopically the sputum contains leukocytes, epithelial cells, bacteria, crystals of different kinds and generally shreads of lung tissue. The latter are sometimes of sufficient size as to be recognized by the unaided eye. Elastic tissue, and black and yellow pigment also occur. The particles of lung tissue constitute the characteristic feature. Fraenkel states the pneumococcus abscesses are larger than those in influenza pneumonia, which are apt to the diminutive and multiple.

The diagnosis, as Skoda long ago pointed out, cannot be made by auscultation and percussion alone. The cases pursue the course of a delayed resolution, with an irregular protracted fever, and at times hectic symptoms. "A probable diagnosis might be made if with the rapid increase of pneumonic symptoms, a large quantity of pus, colored red by blood, should be brought up suddenly, followed by improvement in the phenomena of infiltration; the condition can be established with certainty only after the demonstration of lung tissue in the sputum." The recurrence of fever after crisis, if accompanied by profuse expectoration should always call for a microscopic examination of the sputum.

Gangrene of the Lung.—Pneumonia occasionally terminates in *gangrene of the lung*. This occurred clinically in 136 (0.49 per cent.) of 27,761 collected cases and in 1,914 autopsy reports showed 100 (5.2 per cent.). As in abscess of the lung, alcoholism and general lack of vitality seem to be predisposing factors; among the latter conditions diabetes, nephritis, typhoid fever and insanity deserve to be noted. The etiology of gangrene is uncertain; some cases follow abscess, others occur without it. When gangrene begins we find in the sputum, in addition to various pyogenic microörganisms, different saprophytic bacteria through the agency of which necrosis of the pulmonary tissue rapidly occurs. The first symptom is an alteration in the character of the expectoration, which becomes brownish, more liquid and finally prune-juice or chocolate colored. Microscopically the sputum shows, despite its manifestly bloody character, few, if any, red blood corpuscles, these cells having undergone solution as the result of the putrefactive process. From the same cause the particles of lung tissue are more minute than those found in abscess, they being barely visible to the naked eye. The elastic tissue also is no longer sharply outlined in contour. Hæmatoidin crystals may be encountered. As the morbid process advances the sputum becomes extremely offensive, often to such an extent that the whole room which the patient occupies is tainted with the putrid odor. The amount of expectoration may reach 1,000 cc. per diem. Its color is grayish or greenish; when allowed to stand it separates into three layers, the uppermost containing mucus and necrotic tissue, which float on account of the air they contain; the second layer consists of liquid and the bottom of pus cells and necrotic debris. Bacteria are abundant, and in addition to the already mentioned substances, crystals of fatty acids, of leucin and tyrosin, of cholesterin and pigment may be found. Freshly expectorated sputum is generally alkaline in reaction, by virtue of free ammonia and alkaline salts which it contains;

on standing it becomes acid from fermentative processes, during which butyric and other acids are produced.

Gangrene of the lung is accompanied by constitutional symptoms of great severity, by physical signs of delayed resolution, and if the patient lives long enough, by evidences of cavity formation. Occasionally infection of the pleural cavity produces an empyema, or rupture, a pyopneumothorax, as in a case reported by West. Fœtor of the breath may be absent, as in one of Wells' cases, and in 39 per cent. of those collected by Atkins. It must also be borne in mind that although fœtor is very characteristic of gangrene of the lungs, it may also occur, though to a less extreme degree, in abscess, bronchiectasis, ulceration of the bronchi, etc.

Gangrene occurs chiefly in those advanced in life. In 1872 Atkins was able to collect only 35 cases occurring in infancy from the entire literature. Fraenkel found that 10.6 per cent. of 85 cases of gangrene were due to influenza pneumonia, and that 7.5 per cent. of all influenza pneumonias terminated in gangrene. The proportion of all cases of pulmonary gangrene which arise from pneumonia as reported by different observers is as follows: Sturgis and Coupland, 38 cases of gangrene, 14 had preceding pneumonia; Grisolle, 70 cases of gangrene, 5 had preceding pneumonia; and Hensel, 73 cases of gangrene, 5 had preceding pneumonia. The gangrenous process may begin in an old tuberculous focus, or in a pulmonary abscess. Holt has reported a case in which an occlusion of the artery seemed to be the cause. Wagner has recorded a case in which a sphacelus of lung tissue, one by three inches in size, was found free in the pleural cavity; recovery followed an operation. Sometimes the gangrene is localized to the pleura. The junior author has recently seen pulmonary gangrene follow pneumonia in a man aged forty-seven years, in whom the physical signs were practically negative until very shortly before death, when cavernous breath sounds were heard at the right base accompanied by very slight impairment of resonance. The expectoration was small in amount, yellowish, muco-purulent and homogeneous in character, and devoid of fœtor. The temperature was more or less continuous ranging about 100° F., but the pulse and respirations were both very high. At autopsy practically the whole lower half of the right lung was destroyed.

Historical reports seem to show that gangrene of the lung is much more frequent in certain epidemics. Lepine states that it is more common in certain climates such as India, Malabar and the coast of Coromandel. The two sexes seem to be equally affected. A complete tabulation of the reported cases of gangrene following pneumonia has been compiled by F. W. McRae.[1]

The main hope of recovery in abscess and gangrene of the lung lies in surgical intervention, for although patients undoubtedly do get well without operation, the number is much smaller in the latter than in the former event. Medical treatment can only be symptomatic and is limited largely to the administration of drugs such as creosote, turpentine, oil of sandal wood, etc., which tend to decrease the fœtor of the expectoration, general tonics and stimulants. The following comparisons show what may be expected from the two methods of treatment. Even allowing for the fact that those surgically treated were picked cases, the figures are vastly in the favor of surgery: In a series of 110 cases treated medically there were 79 deaths (71 per cent.), while Eisendrath gives the following statistics after operative interven-

[1] *Journal of the American Medical Association,* vol. xxxix, September 27, p. 739.

tion: of 25 acute simple abscess, 24 recovered (96 per cent.), 1 improved (4 per cent.); of 28 acute gangrene, 20 recovered (71.4 per cent.), 2 improved (7.2 per cent.), 6 died (21.4 per cent.); of 14 chronic simple abscess with bronchiectasis, 6 recovered (42.8 per cent.), 3 improved (21.4 per cent.), 5 died (35.8 per cent.); and of 26 chronic putrid abscess with bronchiectasis, 13 recovered (50 per cent.), 4 improved (15.3 per cent.), and 9 died (34.7 per cent.).

Riesman, Wood and Pfahler have reported a case of gangrene occurring ten days after the onset of pneumonia, diagnosed and localized with the help of the *x*-rays, and treated by resection of the ribs with recovery. Ulatowski reported 2 cases operated on by Helfrich with 1 recovery, the second patient dying, as was shown by autopsy, as the result of constriction of the vena cava by contracting pulmonary tissue. Lejars reported 6 cases, which he has carefully studied, with 2 complete recoveries, 1 formation of fistula, and 3 deaths. Two of the patients who died were very weak before the operation and 1 had pulmonary tuberculosis. He states that three factors are essential for success; localization of the process, pleural adhesions and a large opening. P. Delbert reports a case ending fatally, in which however there were three distinct foci of gangrene. Monod contributes an article dealing with 2 cases, which remained well during prolonged observation. He advises operation even in cases in which there is apparently sufficient expectoration to ensure satisfactory evacuation, provided that the disease can be accurately localized. Treupel reports a boy aged four years who developed gangrene, after abscess due to rupture of an empyema. He was not operated upon until two years after the original illness but notwithstanding made a satisfactory recovery.

Surgery may be expected to yield good results, when the lesion is limited to one lung, when its area is circumscribed and not diffuse, when it is single, not multiple, and when there are pleural adhesions. "It would be very poor surgery to attempt any interference in a gangrenous lung before nature had raised a barrier and limited the disease—that is, before a line of demarcation or separation has formed" (LeConte).

When death occurs as the result of pulmonary gangrene, it may be due either to suffocation, or collapse, both of which are much aided by coincident toxæmia. If recovery ensues, we may find cavities of varying size, dependent upon the amount of tissue destruction, or extensive fibroid induration with cicatricial contraction.

Subphrenic Abscess.—Subphrenic abscess is very rarely a sequel of pneumonia.[1] The diagnosis of "empyema" is usually made. This condition has been reported by Claudius, Hawkes, Beck, Schlinder and others. Winkelmann has recorded a patient invalided for many months, upon whom all manner of diagnoses had been made; the true condition was finally established by the aspirating needle; excellent recovery followed operation. The infection probably occurs through the diaphragm and in many cases pneumococci have been demonstrated in the pus.

Mediastinitis.—Mediastinitis is a very rare complication of pneumonia. It was found in 8 among 363 collected autopsies. Weichselbaum pointed out that in many patients dead of pneumonia, there were evidences of acute in-

[1] The whole literature of this subject has been reviewed by Perutz, *Centralb f. d Grenzen. d. Med. u Chir.*, vol. viii, No. 10, 1905.

flammation in the areolar tissue of the mediastinum, neck and clavicular fossæ, as well as about the œsophagus, cervical vertebræ and trachea. This was corroborated by Foa and Bordoni-Uffreduzzi. Finally, Thue succeeded in isolating the pneumococcus and tracing it from the lymphatics of the pulmonary pleura to the mediastinum and pericardium (Fraenkel). The last-named author has seen in all, 3 cases, 2 of them having other complications; empyema and pericarditis twice; purulent peritonitis, endocarditis and meningitis were also encountered.

In these cases there is often a general pneumococcus septicæmia. Pöhlmann found one case in 129 pneumonias; in this there was also meningitis, pericarditis and peritonitis. Broadbent has reported a case in a boy of twelve years with pneumonia. There had been no crisis, but delirium and high fever continued. Cough was so severe as to require the administration of chloroform. A diagnosis of enlarged bronchial glands was made and later confirmed. Ultimate recovery followed a rupture of the mediastinal abscess into a bronchus. Fernet has reported 2 cases; in both the primary cause was a focus of infection on the surface of the left lung situated on the internal aspect of the superior lobe near the interlobar space. The infection was pyogenic in the first case following pneumonia and septic in the second following pulmonary gangrene. In both, pleurisy with effusion developed, which invaded the whole of the left mediastinal pleura with prolongations into the interlobar space and into the diaphragmatic pleura. The general cavity of the pleura, however, escaped. The diagnosis of mediastinal pleurisy is difficult, for though its existence may be suspected it is not until a careful search for physical signs has been made that a zone of limited dulness with absence of pulmonary bruit gives the diagnosis. In the 2 cases referred to, this zone was close to the vertebral column at the level of the interlobar space. Operation was performed in both cases; the mediastinal pleura was incised and drained.

Occasionally the *bronchial glands* in pneumonia are so greatly enlarged as to cause pressure symptoms, although this is extremely rare. Tardieu has reported a case in which a loud systolic murmur was heard over the great vessels, which seemed to be due to this cause. In 127 autopsies made by Longcope at the Pennsylvania Hospital, Philadelphia, very marked swelling of the bronchial lymph nodes occurred three times.

Gastro-intestinal Complications.—Gastro-intestinal complications are most marked in asthenic cases, and also occur quite frequently as prodromes, especially in children. Collected statistics are as follows:

Complications.	Cases.	Present.	Percentage.
Vomiting	5,047	1,356	26.8
Nausea	991	134	13.5
Constipation	1,459	151	10.3
Diarrhœa	5,336	190	3.5
Tympanites	40	2	5.0
Abdominal pain	1,129	13	1.1
Enteritis	2,789	30	1.08
Intestinal obstruction	673	2	0.29
Gastric ulcer	245 (autopsies in pneumonia.)	2	0.8

Vomiting may result from gastritis, severe coughing, from toxic cerebral irritation or from a complicating meningitis. Organic disease of the

stomach or intestines sometimes occurs. Osler found 1 case of croupous *gastritis* in 100 autopsies. A membranous *colitis* occurred in 1 of 173 autopsies reported by Kerr, and 5 times in Osler's series. The digestion is not as a rule seriously impaired except as the result of injudicious medication. *Diarrhœa* may result from intestinal ulceration or from toxæmia. Remedies calculated to check this symptom should therefore be administered only after due deliberation. *Hemorrhage* from the bowels may occur. Wells states that during an attack of pneumonia, patients harboring *intestinal parasites* often pass them in large numbers. Dieulafoy has described under the name of ulcerative and hemorrhagic pneumococcic gastritis a condition which may be productive of even fatal hemorrhage. It is accompanied by nausea, vomiting and pain, and may terminate in peritonitis. Dieulafoy suggests that in the event of the patient's recovery such erosions may develop into the so-called peptic ulcers. Fraenkel has also met with this condition.

H. Schiller has called attention to *meteorism*, and states that in slight degree it is often present, being favored by restriction of movements of the diaphragm. If considerable in amount it may be due to peritonitis, septic enteritis or toxic paresis. When marked it is one of the most unfavorable prognostic signs. Pneumococci can be found in the peritoneum in practically all cases of pneumonia.

Peritonitis is one of the most serious complications of pneumonia. That this is rare is shown by the statistics of collected cases. It was found clinically in 28 among 8,132 cases (0.34 per cent.) and in 21 among 971 autopsies (2.16 per cent.). Pneumococcic peritonitis may be either primary or secondary, circumscribed or diffuse. According to Lenormant and Lecene there are 74 cases of pneumococcic peritonitis on record. In 29 of these the process was diffuse. In 16 the condition was secondary; under such circumstances the symptoms are often masked by those of the primary lesion. The first case in which the diagnosis was made *intra vitam* by demonstrating pneumococci in the ascitic fluid, was reported by Bozzolo. The only treatment for the circumscribed variety is early incision with ample drainage. This primary isolated form is the most common, especially in children. The sudden high temperature, palpation of an encysted effusion and diarrhœa are the main features. The primary diffuse form presents a syndrome exactly like that of peritonitis secondary to appendicitis. Some recoveries are reported after operation in the secondary encysted form, but no recoveries are recorded from the secondary diffuse variety.

Menetrier and Aubertin have reported a case coming on three weeks after a pulmonary congestion, Nelaton a case which appeared one month after a pneumonia, and de Grancher and d'Audin cases appearing at the termination of a bronchopneumonia. The case of Lenormant and Lecene followed nine days after operation for empyema. Audion has found the peritoneal lesions most marked on the right side, near the liver. Pneumococci were demonstrated on both sides of the diaphragm in a case of abscess of the lower lobe of the right lung. The same occurred in a second case, in which infection could be traced from the pleura to the peritoneum. In the vast majority the extension is direct, without infection through the blood or lymph channels, although this may occur, the only necessary factor being a solution in the continuity of the pleura, and sufficient virulence on the part of the organism.

Burkhart has seen a case occurring twelve days after a pneumococcic empyema. A. Ghon[1] reports 5 cases of pneumococcic peritonitis originating in lesions of the stomach. In 2 of them there was a preceding pneumonia. Of 81 cases of peritonitis collected by Howard, 36 had had pneumonia, (44.4 per cent.). Netter in 162 cases of pneumococcic infection found only 2 in which the peritoneum was involved. Fawcett has reported 5 cases among 182 fatal cases of pneumonia. As a general rule pneumococcic peritonitis is a primary infection or else part of a general septicæmia. The symptoms do not differ from peritonitis due to other causes. From a practical standpoint its chief interest lies in the fact that it may be very closely simulated by the reflex abdominal pain which occurs with considerable frequency in pneumonia, without any peritoneal lesion.

Longcope has recently called attention to the fact that at least as a terminal complication, peritonitis in pneumonia is not so rare as the literature would lead us to suppose. In the last 23 consecutive pneumonia autopsies at the Pennsylvania Hospital, Philadelphia, well-marked peritonitis was noted 5 times. The pneumococcus was recovered in cultures in 3 cases, the streptococcus in 2. Coplin has shown that the diaphragm itself may be the seat of degenerative changes, but this may also occur in septicæmias due to other organisms than the pneumococcus.

Cardiovascular System.—The *cardiac complications* of pneumonia are of extreme importance, not only concerning the immediate outcome but equally regarding the subsequent life and health of the patient. It is now generally recognized that the infectious fevers are capable of exerting permanent and often marked damage upon the heart and arterial system, a damage, which, although it may not be apparent or be overlooked at the beginning, nevertheless institutes a series of changes which make themselves evident at first through diminished capacity and later through manifest degenerations of the cardiovascular system. The effects of pneumonia upon the heart itself may be brought about through the toxæmia or by the microorganisms themselves. In the former instance the damage is more apt to be of a transient nature, which if the disease itself be overcome, the course of time will remedy. The latter is more apt to leave behind a permanent organic lesion, the usual tendency of which is to become progressive.

Endocarditis.—As Bouillaud first pointed out, pneumonia is one of the causes of endocarditis. Since then acute endocarditis has been ascribed to pneumonic infection with the following frequency: Abraham, 1 out of 9; Banti, 8 out of 22; Desse, 14 out of 34; Harbitz, 9 out of 43; Traux, 1 out of 6; Kanthack and Tickell, 14 out of 84; Lenhartz, 5 out of 38; Osler, 54 out of 209 (ulcerative); Jackson, 1 out of 5; Walter, 1 out of 21; and Weichselbaum, 6 out of 33. Pneumococci were first demonstrated in the valvular lesions of acute endocarditis by Meyer in 1887.

Acute endocarditis occurred in 144 of 32,349 collected cases (0.44 per cent.), and in 157 of 2,639 autopsies (5.8 per cent.). The discrepancy between these figures shows that endocarditis is frequently overlooked. Pneumococcus endocarditis differs in several respects from other varieties of this condition. It is twice as common in women as in men and about three-fourths of the cases are ulcerative in character. Among 16 cases found by Osler in 100 autopsies, 5 were simple and 11 ulcerative; chronic endo-

[1] Ghon, *Wien. klin. Woch.*, 1904, p. 267.

carditis occurred in 21 out of 80 cases. The left heart is more often attacked than the right, but the right is more frequently diseased than is the case in other varieties of endocarditis. Netter found lesions in the right heart in one-seventh of his cases. "To put it another way: In 17.8 per cent. of the cases of pneumococcus endocarditis the right heart is affected, while only 6.7 per cent. of the cases of endocarditis in general are right sided" (Preble)[1]. The aortic and pulmonary valves are oftener diseased than the mitral and tricuspid. Wells found *cardiac thromboses* more frequently than in any other disease, 169 instances of antemortem clot in 777 autopsies (21.7 per cent.). *Infarction* takes place in about one-half of the cases; not rarely as is generally stated. About 60 per cent. of the cases are associated with meningitis, but when the latter is the primary complication, it is accompanied by endocarditis in about 30 per cent.

The exact distribution in Preble's cases was as follows:

		Per Cent.
Aortic only	56	39.7
Mitral only	40	28.3
Aortic and mitral	20	14.1
Tricuspid only	12	8.5
Pulmonary only	5	3.5
Aortic, mitral, and tricuspid	5	3.5
Mitral and tricuspid	2	1.4
Aortic and tricuspid	1	0.7

In Jürgensen's collection we find:

	Per Cent.
Aortic only	18.7
Mitral only	66.3
Aortic and mitral	9.2
Tricuspid only	0.4
Pulmonary only	2.3
Aortic, mitral, and tricuspid	1.0
Mitral and tricuspid	1.8

Aufrecht gives the following data regarding the distribution in relation to age, as well as the distribution of pneumonia itself:

	Pneumococcus Endocarditis.		Pneumonia.	
Decade.	Per Cent.		Per Cent.	
First	2— 1.4		6.8	
Second	8— 5.7	11.9	22.2	58
Third	15—10.8		29.0	
Fourth	42—30.4		17.0	
Fifth	27—19.5	70.9	13.0	35.5
Sixth	29—21.0		5.5	
Seventh and over	15—10.8		6.0	

Acute endocarditis therefore is much more common over thirty years of age than in earlier life. It seems that patients with chronic endocarditis are more likely to develop an acute infection than those in which the endocardium is healthy. Among 945 cases of pneumonia, Sears and Larrabee

[1] Preble, *American Journal of the Medical Sciences*, November, 1904, has collected 132 cases of pneumococcus endocarditis from the literature. From this excellent monograph many of the data have been taken.

found chronic endocarditis in 80, of which 4 came to autopsy; 3 had acute endocarditis. As is the case with other complications, endocardial infection is more apt to occur in alcoholics and otherwise debilitated individuals. Acute endocarditis may occur in animals experimentally inoculated with the pneumococcus but generally only if the valves have been previously injured. About 25 per cent. of Preble's patients had a history of antecedent valvular lesions.

Acute endocarditis is very readily and frequently overlooked, owing to the fact that in the majority of cases physical signs are absent, and when such exist they are generally overshadowed by those of the pulmonary disease itself. Systolic murmurs are very common in pneumonia, and those which are due to acute inflammatory lesions are in no way characteristic. As in other diseases diastolic murmurs are very suggestive, particularly since in pneumonia the valves at the base are so often affected. The most suggestive and often the only positive features of this condition are symptoms referable to infarction of different organs. If the spleen is affected we may find enlargement, pain and tenderness, if the kidneys, pain and hæmaturia, if the lungs, pain, bloody sputum and signs of consolidation, if the skin, petechiæ and ecchymoses. Boston has reported a case of acute endocarditis in pneumonia in which there was a small pneumococcic abscess in the wall of the right ventricle. Blood cultures may be of assistance in arriving at a correct diagnosis; Preble collected 9 cases in which this procedure had been positive, in some of which more than one attempt was necessary. Acute endocarditis complicated by abscess of the thyroid gland has been reported by Schlender.

The symptoms of pneumococcus endocarditis are similar to those of other varieties. Fever is generally present, may be continuous with that of the primary process, intermittent, or accompanied by afebrile periods of varying duration. Chills and hectic symptoms are by no means rare but prolonged apyrexia is not unknown. In the case reported by Lesage and Pineau,[1] which lasted three months, there was complete absence of fever. The average duration of the fever in 109 of Preble's cases was thirty days; the extremes were seven and one hundred and eighty days. The pulse is subject to wide fluctuations, being in some cases very rapid, in other cases slow. Bradycardia may be the result of a complicating meningitis, but may also arise from other causes. Bramwell has reported a case in a man aged sixty-four years with aortic stenosis, terminating fatally on the seventh day, in which the pulse was never above 64. On the last day the temperature was 100, the pulse 56 and the respirations 39, a ratio of $1\frac{1}{2}$ to 1. The pulse rate often varies greatly from minute to minute and is much affected by change of posture.

The prognosis is extremely grave. In Preble's 132 cases there were but four recoveries and in one of these the diagnosis was in doubt. It is likely that unrecognized cases recover more frequently and indirect evidence of this is found in the fact that many cases of chronic endocarditis, in the absence of other previous infectious fevers, give a history of an antecedent attack of pneumonia.

In 20 cases of pneumococcus septicæmia, Lenhartz found 10 of acute endocarditis (50 per cent.) and Roemheld found about the same proportions.

[1] Lesage and Pineau, *Comptes Rendus, Soc. Biolog.*, 1893, p. 124.

Weichselbaum in 14 cases of ulcerative endocarditis found the pneumococcus in 3, and Harbitz in 3 among 39 cases of endocarditis.

As to the effect of *chronic endocarditis* upon pneumonia, Hay states that in well-compensated cases, the course of the disease is unaffected, except that delayed resolution is apt to occur. The writer's investigations lead to different conclusions. Of 114 cases of pneumonia complicated by chronic endocarditis 37 or 32.46 per cent. died, a figure certainly above the average mortality, although it must be borne in mind that a number of these cases were advanced in life and probably the subjects of renal disease.

Pericarditis.—*Acute pericarditis,* either serous, plastic or purulent, occurred 268 times among 2,128 autopsies (12.6 per cent.), and 499 times among 40,773 collected cases of pneumonia (1.2 per cent.). It is therefore by far the commonest cardiac complication and stands high up among complications in general. The wide variation in the frequency with which the condition is reported by different observers shows that even allowing for errors the condition is more frequent at certain times.[1] That pericarditis is frequently found unexpectedly at autopsy is well known. Friction sounds over the precordium are often transient and of short duration. Furthermore they are often obscured by rales, the breath sounds, and pleural friction.

Infection may occur through the blood or the lymph streams, but quite often results from direct extension from infected areas of the lungs and pleuræ. In a large proportion of Jürgensen's cases the lingual process of the left upper lobe was diseased. Sears and Larrabee found the right lung diseased in 10 out of 18 cases. Chatard noted the right lung in 13, the left in 5 and both lungs in 13. Kerr found the left lower lobe involved in 12, the right lower in 9, the right middle in 2 and both lower in 3 cases. J. A. Scott in 76 autopsies on lobar pneumonia at the Pennsylvania Hospital, Philadelphia, found pericarditis in 38 or 50 per cent. In 20 or 52.56 per cent., the exudate was sero-fibrinous, in 17 or 44.7 per cent., purulent, and in 1 case the pericardium was obliterated by chronic inflammation. Among 40 cases of pericarditis 22 occurred in pneumonia, in all of these pleuritis co-existed, and in 6 cases both the pericarditis and the pleuritis were fibrino-purulent. In 170 autopsies in pneumonia, Lange and Kanthack found pericarditis 37 times. It was associated with the following conditions: acute endocarditis 4, pleuritis or empyema 8, peritonitis 1, meningitis 1, synovitis 1, pleuritis and peritonitis 2, meningitis and peritonitis 1, pleuritis and endocarditis 1. Chatard found the pneumococcus in the pericardium in 19 out of 29 cases, no other important organisms being cultivated.

Dietl has endeavored to show that venesection greatly increases the frequency of pericarditis but the number of cases upon which he based his deductions was too small. Pericarditis may appear during any stage of the disease but does so most often during the fastigium. The onset is unaccompanied by any characteristic symptoms or signs. The heart should be examined with care daily but even under these circumstances, detection may be impossible. The symptoms are similar to those of pericarditis due to other causes. The temperature may be normal and if present as the result of the primary disease it may be depressed by the presence of a purulent exudate. The seriousness of the prognosis is materially enhanced by this complication, which interferes both mechanically and by being associated

[1] Netter found pericarditis in pneumonia during the years 1837, 1876, 1882, 1886 and 1890 much more frequently than in the intermediate years.

with myocarditis. Among 207 cases, 125 died (60 per cent.). In 55 fatal cases of pneumonia Satterthwaite found that in 10 instances death was directly attributable to pericardial involvement.

Treatment should consist of the local application of cold to the precordium, and such other measures as the individual case may require. As soon as the presence of an effusion is even reasonably established, an exploratory puncture should be made and if the exudate prove purulent in character the patient should be turned over to the surgeon for resection and drainage as this offers the only hope of recovery.

Vascular Lesions.—A fairly large number of cases of peripheral venous thrombosis are recorded in the literature. Steiner has reported 3 and collected 38 instances. He states that the condition is usually a sequel, though it may come on at any time. Of 41 cases, 9 died, 25 recovered, in 7 there were no data. In 5, death was due to pulmonary embolism. The condition is rare, despite the fact that in pneumonia the blood is rich in the elements which favor clotting. The lower extremities are nearly always the seat of involvement and the left side more often than the right, owing to the anatomical conditions. Ashton and Landis in 991 cases of pneumonia found 1 case of thrombosis of the external jugular and axillary veins, which terminated in death. Dosi saw a case in which a thrombosis of the ascending vena cava was imperfectly compensated. J. N. Hall reported a case involving the cervical veins. Pulmonary thrombosis is one of the causes of sudden death in pneumonia. Doubleday found 1 such case in 252 pneumonias. The junior author found 1 case of pulmonary thrombosis in 127 autopsies. Other vascular lesions were: infarct of the lung 2, of the kidney 3, of the spleen 7. Among our collected cases pulmonary thrombosis occurred 5 times in 1,830 pneumonias, (0.27 per cent.), and peripheral thrombosis 17 in 2,360 (0.72 per cent.).

Kredel's case of popliteal thrombosis necessitated amputation. Seidelmann saw symmetrical gangrene in the fingers and thumbs of both hands, in a female of 29 years, who developed double pneumonia 29 days after giving birth to twins. Hjelt has reported embolism of the abdominal aorta.

Embolism of the right lenticulo-optic artery was encountered by Aldrich. As a result of embolism one sometimes meets with spontaneous gangrene of the extremities. Cases recorded show that the legs, fingers and toes have been lost; in some amputation was performed, in others spontaneous sloughing took place.

Renal System.—Albuminuria.—Albuminuria was found in 2,184 of 4,792 collected cases (45.58 per cent.). Exclusive of these figures transient albuminuria has been reported with the following frequency: Fraenkel and Reiche 42.6 per cent., Rosenstein 23.1 per cent., Craemer 68.18 per cent., Bleuler 52 per cent., Morhart 37 per cent., Pöhlmann 37 per cent., Stoertz 52.1 per cent., Petzold 14 per cent. Of 1,353 cases with albuminuria, 430 died (31.78 per cent.), of 628 cases without it 62 were fatal (.87 per cent.). According to Fraenkel and Reiche the condition bears some relation to the extent of the pulmonary involvement. When only one lobe was diseased they found 39 per cent., when large areas were consolidated, 54 per cent. The albuminuria also seems to be more frequent in cases ending by lysis.

The vast majority of these albuminurias are transient in character, and accompanied only by a few hyaline casts, epithelial cells and leukocytes; occasionally red cells are found, these representing a higher grade of renal

irritation. It is not possible to make a sharp distinction between the so-called "febrile albuminuria" and mild grades of *nephritis*. Both Senator and Aufrecht hold that the matter is simply one of degree, both processes being caused by the same factors, namely the presence of microörganisms[1] or their toxins in the kidneys. When the organisms are numerous or the toxins virulent severe grades of nephritis may be produced. The question must therefore be decided largely by the duration. If the albuminuria is simply due to the fever, it will disappear with, or soon after, the crisis. The albumin and casts occurring as the result of acute nephritis are in no wise different from those encountered in other varieties of acute inflammation of the kidney.

Nephritis.—In 30,042 collected cases, acute nephritis occurred in 367 (1.2 per cent.) and in 1,334 autopsy reports, it was noted in 255 (19 per cent.). Of 116 cases of acute nephritis in pneumonia, 76 died (65.52 per cent.). Nephritis may come on at any stage of the disease. Uræmia and œdema are uncommon symptoms; hæmaturia is frequently encountered. The usual termination is in death or recovery, chronic nephritis being an unusual outcome. V. Leyden, Eisenlohr, Fraenkel and Reiche, have each reported one such event. Among 489 cases of pneumonia the senior author found nephritis 92 times, of which 55 died (59 per cent.). Acute nephritis occurred 6 times, 4 being fatal (66 per cent.). Among 127 pneumonia autopsies collected by the junior author from the records of the Pennsylvania Hospital, Philadelphia, the following pathological conditions were found: cloudy swelling in 45, acute nephritis in 18 and chronic nephritis in 53. Hæmoglobinuria has been reported by Nash.

In 275 autopsies on patients dead of pneumonia at the Philadelphia General Hospital, Anders found renal lesions in 90.5 per cent., occurring as follows: chronic interstitial nephritis 145 (52.7 per cent.), chronic parenchymatous nephritis 50 (18 per cent.), acute nephritis 38 (13.8 per cent.). It must be borne in mind that in this hospital the majority of the patients are advanced in life and the subjects of arterial or other chronic disease. Among the remaining 25 cases, 1 had a renal calculus, 1 tuberculosis of the kidney, and most of the rest subacute nephritis. Pneumonia occurs very commonly as a terminal infection in chronic nephritis, and individuals with this and arteriosclerosis are apparently more likely to have lobar than bronchopneumonia as a terminal infection. In 195 carefully studied autopsies on cases of pneumonia, Howard found in 36 cases of secondary lobar pneumonia that arteriosclerosis was the most marked chronic lesion in 10 and nephritis in 3, whereas in 124 cases of secondary bronchopneumonia, arterial degeneration was the most conspicuous lesion in 12 and chronic nephritis in 3.

Our collected statistics are as follows: *Abscess of the kidney* was found in 3 (0.25 per cent.) among 1,194 and *renal calculus* in 2 patients among 708, both of whom died. *Orchitis* was found in 2 among 930. In 72 autopsies 1 had *hydronephrosis* and 1 *pyelitis*, in 573 autopsies 148 (25.8 per cent.) had *chronic nephritis* and in 172 autopsies 3 had *renal abscess*. *Retension of urine* occurs occasionally, but it seems unlikely that the pneumonia has any direct effect upon the condition.

The Skin.—The skin in pneumonia may show various processes, but the majority are simply the result of coincidence. Thus erysipelas is occasionally

[1] Fraenkel and Reiche found the pneumococcus in the kidneys in 22 out of 26 cases.

encountered. Among 489 cases the senior author found erysipelas in 1, eczema in 1, urticaria in 3, furunculosis in 1. The junior author found 2 cases of erysipelas among 127 autopsies. Collected cases give the following data:

Condition.	Cases.	Occurrence.
Erysipelas	8,043	32
Loss of hair	1,065	1
Furuncles	230	5
Purpura	949	1
Erythema multiforme	500	1
Petechiæ	486	1
Ecthyma	133	1
Herpes zoster	1,065	2

Underwood has reported a case of purpura hæmorrhagica as a sequel of pneumonia, in which there was also delayed resolution, arthritis of the left ankle, erythema, persistent epistaxis and melæna. An instance of pneumococcic metastatic dermatitis has been recorded by Wolkowioz. Desquamation has occurred, Campani having reported a number of cases. The latter condition occurs during convalescence on the face, principally on the nose and cheeks, and is probably analogous to the desquamation in typhoid fever.

Jaundice.—The marked diversity of opinion as to the frequency of jaundice in pneumonia is to be explained by the fact that slight degrees are easily overlooked and that its occurrence varies greatly in different epidemics. Regarding its pathogenesis, numerous theories have been advanced. Venous stasis has been suggested but this is rarely sufficient to account for the icterus, nor is stasis in other organs often found. Again stagnation of bile resulting from restricted excursions of the diaphragm is an unsatisfactory explanation, as in this case jaundice should be much more common when the right lower lobe is involved, but according to Petrow, who has especially studied this point, jaundice occurred only in 6 of 57 right-sided pneumonias.

Banti from a study of 15 cases concluded that hæmolysis was brought about by the pneumococcus. His cases at autopsy showed patent bile ducts, inspissated bile and bile stained fæces. Microörganisms from these patients when injected into animals produced hæmoglobinuria, those from others in which no jaundice existed failed to do so. Lately a number of writers have reported cholecystitis, duodenitis and catarrh of the smaller bile ducts. When the jaundice is marked, nearly all observers have encountered a high mortality: Mosler 73 per cent., Fismer 20 per cent., Musser 25 per cent. and Norris 61 per cent. As Preble suggests, this high mortality is probably not alone dependent upon the actual intensity of the icterus, but also upon the etiology. These patients usually manifest all the symptoms of severe cholæmia, and according to some French authorities very often have dilatation of the heart. Albuminuria is often caused or if already present is intensified by cholæmia, and the sputum may be of a greenish hue.

Much discussion has been carried on concerning the so-called "*bilious pneumonia*," a form of the disease not necessarily associated with icterus, but accompanied by marked nervous and gastro-intestinal symptoms, prostration and a high mortality. It was originally described by Stoll and by Traube, and corresponds more to what is now characterized as asthenic or typhoid pneumonia. The term "bilious pneumonia" should be dropped, it being but a poor description of uncertain forms of pneumonia.

Jaundice probably arises from a variety of causes: retention of bile, infection of the gall ducts, gall bladder or liver, hypostatic congestion, toxæmia and hæmolyis, the latter being of considerable importance. When cholecystitis is present, its symptoms are apt to be overshadowed by the primary disease. The character of such infection varies; in Gilbert and Grenet's cases it was the colon bacillus, in Clairmont's case, Friedländer's bacillus. Changes in the hepatic parenchyma, cloudy swelling, etc., may cause a perversion of function, in the same way as the renal epithelium may permit the passage of albumin. The consensus of opinion however seems to be that there is no direct relation between the pneumonia and the jaundice, other than an accidental complication which occurs with greater frequency among alcoholics.

Enlargement of the Liver.—Enlargement of the liver is quite often encountered, the edge being palpable a short distance below the costal margin. This may result from actual enlargement, the result of cloudy swelling, or may be only apparent, being merely a displacement downward, produced by massive consolidation of the right lung, pleural exudate or subdiaphragmatic abscess. Gilbert and Grenet studied the size of the liver in 48 cases and found it palpable below the costal margin in one-fourth of the adult cases and in all instances among children, but not so in those of advanced age.

The collected statistics of hepatic complications are as follows: Of 22,544 cases, 373 or 1.65 per cent. had jaundice and of 344 so affected, 54 or 15.7 per cent. died; of 173 patients, 35 or 20.23 per cent. had a palpable liver, in 7 of whom the liver was tender; of 201 patients, 1 had perihepatitis and 1 had liver abscess; of 3,644 patients, 19 (0.52 per cent.) had cirrhosis of the liver; of 500 patients, 1 had acute hepatitis and of 991, 1 had carcinoma of the gall bladder; of 949, 1 had a gumma and another a distended gall bladder. Of 144 autopsies 8, or 5.55 per cent. showed nutmeg liver; of 517 autopsies, 26 or 5.03 per cent. showed cirrhosis; of 216 autopsies, 115 or 53.24 per cent. showed fatty liver; of 72 autopsies, 1 had stenosis of the hepatic duct; of 293 autopsies, 158 or 52.9 per cent. had acute parenchymatous hepatitis; of 400 autopsies, 9 or 2.25 per cent. had jaundice; of 173 autopsies, 5 or 2.89 per cent. had gummata and of 127 autopsies, 2 or 1.5 per cent. had cholecystitis.

It is to be noted that the mortality in the cases complicated by jaundice is decidedly low, this being opposed to the statements generally made in text-books dealing with the subject, and showing that the icterus *per se* is not an unfavorable factor.

Nervous System.—Complications in the nervous system may be very varied It is often difficult to determine just what relation the pneumococcus bears to the nervous system. For instance, Seitz has succeeded in cultivating this organism from the central nervous system of a patient dying of Landry's paralysis, who had no other evidences of such infection.

Meningismus is quite common in pneumonia, especially in childhood. This condition may arise from a variety of causes,—reflex, toxic, febrile otitis media—other than pneumococcic infection of the meninges. Primary pneumococcus meningitis may of course occur, but in the present article we are chiefly interested in the secondary variety following pulmonary lesions.

Meningitis.—Among 49,028 collected clinical cases meningitis occurred in 206 (0.24 per cent.), and at autopsy in 180 out of 4,833 (3.5 per cent.).

Aside from children, meningitis occurs chiefly in those debilitated from different causes. Fox collected 29 cases; 9 were in drunkards, 7 in red and 19 in gray hepatization, 8 had empyema, and 1 suppurative parotitis; most of them occurred between the third and the seventeenth day.

The duration of symptoms was one day in 22 cases, two days in 19 cases, three days in 7 cases, four days in 6 cases, five days in 3 cases, six days in 1 case, seven days in 3 cases, eight days in 2 cases, nine days in 1 case and eleven days in 1 case (Netter).

The day of onset was on the third day in 1 case, fourth day in 1 case, sixth day in 4 cases, seventh day in 1 case, eighth day in 2 cases, ninth day in 3 cases, tenth day in 6 cases, twelfth day in 2 cases and seventeenth day in 2 cases (Nauwerk).

Meningitis seems to be pretty evenly distributed between the sexes, when allowance is made for the greater number of cases of pneumonia which occur in men. Netter found 90 cases in males to 39 in females. The majority occur in the third, fourth and fifth decades. Among the cases of this author, 26 per cent. were under twenty-five years, 44 per cent. between twenty-five and fifty years, and 30 per cent. over fifty years of age. As in other complications, meningitis is more common in certain epidemics. In Dorpat for instance, Meyer found 5 cases among 11 autopsies.

The majority of the cases occur during the acme of the disease. Infection may take place through the blood, lymphatics, the areolar tissue beginning in the mediastinum and extending upward to the nose, accessory sinuses, or ethmoidal fenestrations. Nauwerk found the convexity of the brain involved 4 times, the convexity and base 16 times, the convexity, base and spinal cord, 7 times. The distribution of the inflammatory process and exudate accounts for the great diversity of symptoms. Fraenkel has called particular attention to the fact that in pneumococcic meningitis the onset, and even the entire course, may be insidious. This was particularly the case in adults and occurred in 4 of his 5 cases, in one of them even rigidity of the neck was entirely absent. The earlier in the course of the disease the meningitis appears, the more striking are the symptoms.

In 489 cases of pneumonia the senior author found retraction of the head without meningitis in 3, headache in 10, stupor in 23, delirium in 77, subsultus tendinum in 16, convulsions in 5, hiccough in 1 (fatal), delusions and hallucinations in 1. Dally has reported paralysis of the ocular muscles of the right eye, which was turned upward and outward, in a girl aged eleven years. Lumbar puncture was negative and recovery ensued.

The symptoms when present are those of meningitis due to other infections, headache, vomiting, cervical rigidity and retraction, and delirium. If no more than these are present it may be impossible to decide whether we are dealing with a meningitis or not. The diagnosis must generally be based upon the appearance of more definite symptoms such as neuroretinitis, paralyses of the cranial nerves, etc., slowness of the pulse, monoplegias or hemiplegias. Generally the question may be definitely settled by lumbar puncture. In some cases the cardinal symptoms from the very time of onset are those of meningitis, definite signs of pneumonia making their appearance several days later. Here the interesting question suggests itself, as to the relationship of the pneumococcus to the meningococcus, and of pneumonia to cerebrospinal meningitis, and as to whether the portal of entry in the last-named disease may not be the lung. Four cases of cerebro-

spinal meningitis apparently due to the pneumococcus have been reported by Willson. Occasionally the meningitis appears a long time after the pneumonia, as in a case reported by Aufrecht, in which it appeared two months after recovery from a pneumonia complicated by empyema, in which there had been no cerebral symptoms during the primary attack. The presence of meningitis adds very much to the seriousness of the disease. Undoubtedly some cases do recover, but in these there is the suspicion that we may have been dealing with symptoms only and not with organic disease. All of Nauwerk's cases died. Of 33 cases collected by the writers, 31 or 93.93 per cent. were fatal.

Hemorrhagic encephalitis has been described by Weichselbaum.

Coma and Stupor.—Coma and stupor may occur in pneumonia. They are unfavorable symptoms which occur most frequently in toxic cases and in children; they may be associated with headache, vomiting and rigidity of the neck without there being a meningitis present.

The condition of the *pupils* has been studied by a number of observers, without any definite conclusions being reached. Zanoni found mydriasis quite frequently; he attributes it to the action of the antitoxin, and considers its absence prognostically unfavorable. Sighicelli found dilated pupils frequently but considers it an unfavorable omen. He also found inequality quite often, the larger pupil being usually on the side corresponding to the pulmonary lesion. This may be due to toxæmia but more probably results from reflex irritation of the superior cervical sympathetic ganglion through inflammation about the pulmonary branches of the vagus. Eason observed mydriasis on the side of the lesion in 24 out of 54 cases. The junior author examined 64 patients with especial reference to the pupillary condition but found inequality only twice, although the upper lobe of the lung was involved in 33. In one case there was mydriasis, in the other myosis, of the affected side. Pupillary inequality is by no means infrequent in healthy people, whose eyes differ in refractive power, this being especially the case when myopia and hypermetropia co-exist. Furthermore it is quite common for the pupil nearer the source of illumination to be smaller than the other, so that we must eliminate a number of causes before ascribing pupillary abnormalities to pneumonia. Schultze has reported temporary absence of the light reflex.

Neuritis.—Neuritis as a complication or sequel of pneumonia has been reported by a number of observers. The diversity of the nerves involved suggests that the etiological factor is a toxic one. Aldrich has reported neuritis of the brachial plexus following pneumonia, resulting in atrophy of the trapezius, spinati, deltoid and supinator longus muscles. The pain in the shoulder associated with the neuritis was preceded by a severe attack of singultus which came on during convalescence and lasted five days. He believed that the neuritis began in the phrenic nerve. Brachial neuritis occurring during the attack is reported by Leszynsky. External oculomotor paralysis in apical pneumonia, disappearing with resolution, without cerebral symptoms and probably toxic, has been recorded by Voute. A case of left-sided ulnar neuritis following pneumonia on the same side, was observed by Rouger. The senior author found 1 case of bilateral ulnar neuritis among 415 pneumonias. Multiple neuritis as a sequel has been recorded by Conner, in whose patient, three weeks after the onset of a pneumonia, extensive, almost complete, paralysis of the extensors of the leg

and left arm, with slight loss of power in the right arm, without anæsthesia occurred. There was numbness of the finger tips, anæsthesia over the crests of both ilia, and girdle sensations, but otherwise no sensory disturbances. One week later complete paralysis of the diaphragm appeared and lasted six weeks; fair recovery followed.

Renon and Gerandel report two cases; in the first, ulnar neuritis appeared two days after the crisis and lasted two weeks with ultimate recovery; the second patient was severely toxic. C. Doering has reported a case of neuritis; four days after the crisis a secondary rise of temperature occurred with defervescence by lysis; during the latter period the left vocal cord, the facial nerve, and the left side of the palate became paralyzed. Boulloche has reported 3 cases of paralysis of the palate; in 1 of them there was also a neuritis, both sensory and motor, of all four extremities. Recovery in these cases is the rule. He has collected 56 cases of paralysis occurring in pneumonia, most of which were of the hemiplegic type. In childhood most of them ended by recovery, in advanced life by death. Krafft-Ebbing reported a case of bilateral neuritis of the upper extremities coming on suddenly with loss of power, anæsthesia to the elbows, and hyperæsthesia of the fingers. Pirrone has demonstrated by experimental researches that the pneumococcus can produce an ascending neuritis, but that the nerves are not an easy route for the propagation of the inflammatory process toward the centres. The lesions grow less and less pronounced as they recede from the periphery.

Hemiplegia.—Hemiplegia in pneumonia may be embolic or toxic. Becker found 1 example of the former among 505 pneumonias in German recruits. Transient hemiplegia and aphasia during convalescence have been reported by Antoniu. Transient aphasia has also been recorded by Chantemesse and by Isager. The patient of the latter was a boy aged nine years; the aphasia lasted for two weeks. It is of course possible that these evanescent lesions have uræmia as a cause. In a case of hemiplegia with aphasia reported by Vogelius the condition was brought about by necrosis of cerebral tissue. In 5 cases of tardy paralysis following pneumonia, meningomyelitis was found in 2, while the others presented no such lesion. *General paralysis* has been reported as a sequel of pneumonia, by Gubler and by Macario. Tetanoid and choreiform manifestations occurring in man and wife, both the subjects of pneumonia, have been described by Kelynack, and *tetany* two weeks after pneumonia in a rachitic girl by Page.

Ocular Complications.—Ocular complications are occasionally seen. Two cases of conjunctivitis occurred in 141 cases. Becker in 505 pneumonias found 1 case of conjunctivitis and keratitis. Pneumococcus conjunctivitis is well known to ophthalmologists. Mandl has reported a case of keratitis with perforation of the cornea on the fourteenth day; the cultures showed pneumococci. Transient mydriasis, photophobia, and amblyopia have been described by Thomas, and distention of the retinal veins by Sichel, and Seidel.

Acute Otitis Media.—Acute otitis media occurs chiefly in childhood and may appear at any stage of the disease. The two conditions may be simple coincidences, infection of the ear may come through the Eustachian tube or the blood, the pneumonia may be secondary to disease of the ear, or the otitis may cause general sepsis and a septic pneumonia follows. According to Lermoyer and Helme hæmatogenous infection gives rise to more virulent

inflammations, which is corroborated by the fact that in cases of general pneumococcus infection, extensive suppuration is apt to occur. Wells states that "One or both ears may be affected; rupture of the tympanic membrane is the rule; severe mastoiditis may occur; extension to the cerebral membranes or sinuses is rare. In these cases the mental dulness increases; pseudomeningeal symptoms may appear; rigidity of the neck is often, if not usually, present; tenderness is manifested when pressure is made on the lobe of the ear; recovery without impairment of hearing is the rule." Right-sided pneumonia is said to be more frequently complicated by otitis media. Among collected cases: Of 4,885 patients, 62 (1.3 per cent.) had suppuration of the middle ear; of 1,065 patients, 1 had suppuration of the external ear; of 949 patients, 2 (0.2 per cent.) had mastoiditis; of 500 patients, 2 (0.4 per cent.) had pain in the ear at onset; and of 1,305 patients, in 8 (0.6 per cent.) more or less deafness followed. Among 54 autopsies otitis media was found in 4 (7.4 per cent.). Exclusive of these cases, Hall found otitis media once in 70, and Futcher once in 48 pneumonias. Metastatic pneumonia following otitis media has been reported by Hrach. Otitis media would be found more commonly if the middle ear were routinely examined at autopsy. Netter found otitis in one-fourth of all his cases. Whenever symptoms suggestive of meningitis occur in pneumonia, an examination of the ears should be made; such symptoms have been known to disappear rapidly after puncture and drainage of the tympanic cavity. Mastoiditis requiring operative intervention has been reported by Schwartze.

Acute Parotitis.—Acute parotitis is a rare complication. In the literature references were found to 20 cases of parotitis complicating pneumonia. Among 2,655 collected cases it occurred in 10 (0.37 per cent.). The junior author found 1 case of suppurative parotitis in 127 autopsies. It generally occurs late in the course or as a sequel, as in the instance reported by Fischel, which came on with fever twenty days after the crisis, and fourteen days later ruptured into the mouth. Pneumococci were cultivated from the pus, while the duct of the opposite gland was sterile. Claisse and Duplay have shown experimentally that a healthy parotid duct cannot be infected by smearing the opening or introducing microörganisms into the lumen. An ascending infection can be produced if the organisms are excessively virulent or numerous, if the general vitality of the animal is reduced, or if the normal secretion of the gland is altered or diminished.

The symptoms consist of tenderness, swelling, painful secretion of saliva, a dry mouth, an increase of fever, and often a chill. The inflammation reaches its height in four or five days, and may abate or suppurate. The pus may drain into the mouth or rupture into it. As a sequel sepsis, fistula, destruction of the maxillary joint, necrosis of the bone, ulceration of the jugular vein with resultant hemorrhage or thrombosis, paralysis of the facial nerve, or a burrowing of pus into the middle ear or mediastinum may occur.

Acute Arthritis.—Acute arthritis as a complication of pneumonia has long been recognized, but was classed by the older writers as "rheumatism." It is now universally considered a true pneumococcic complication. Grisolle was the first to point out the similarity of this condition to the arthritis in pyæmia and to suggest the same etiological factor as causative both of the pulmonary and the joint involvement. Arthritis may appear at any stage, involve one or more joints, and attack conjointly or individually the synovial membrane, bursæ or joints. Cave has collected 30 cases of which 23 died.

Two varieties are to be distinguished, the serous and the purulent. Fever, pain, local swelling and redness are much more marked in the latter variety, in fact in the former these may be very slight indeed. The onset of the joint invasion is occasionally heralded by chills and elevation of temperature. Among 22 cases collected by Brunner, 11 were monarticular, the shoulder being most often attacked. Recovery may take place, even in the suppurative form, without much local injury. Tournier and Courmont, however, believe that actual destruction of bony tissue occurs more frequently than is generally appreciated. Miller has reported a case, at first sero-purulent, later purulent, which recovered completely without operation under local applications and subsequent massage. Cave believes that all purulent cases should be treated by incision, flushing and drainage. This form has a very heavy mortality, not from the local condition alone, but because it often bespeaks a severe infection. Six of Brunner's patients had acute endocarditis. Infection is usually by the blood stream in simple cases as well as in those in which mixed infection exists. It may, however, be carried by the lymphatics, as in the 29 cases of multiple suppurative, pneumonic metastases studied by Bloch. Primary pneumococcus arthritis of the knee joint has been reported.

Among 28,040 collected clinical cases, acute arthritis occurred in 150 (0.5 per cent.), and in 4 of 698 autopsies (0.57 per cent.). Septic arthritis occurred twice in 673 cases. Among 737 cases of pneumonia reported by Morhart, Moosberger and Fricke, there is no reference to this condition. In many of the reported cases there was no bacteriological examination. In 1903, Howard added a number to those previously collected, and found the total number reported up to that date to be 72.

Herrick,[1] who has made an elaborate study of this condition, states that pneumococcic arthritis is a rare affection, found oftener in men and sparing no age. It appears oftenest during or shortly after lobar pneumonia, but has come on three weeks after the crisis. It may be primary in the joint, and severe, even fatal, constitutional symptoms may result from the toxæmia thus induced. In these primary cases involvement of the lungs may or may not occur. Previous damage to the joint by trauma, rheumatism or gout favors infection. The lesions may be limited to the synovia, or may involve the cartilages and bones as well. The periarticular structures may be involved. The subacute cases are sometimes highly destructive to the joint and the same is true of some of the acuter ones. The lesions are monarticular in over 60 per cent., the larger joints being most often involved. The joints of the upper extremity are but slightly more often affected than those of the lower. The condition presents the usual symptoms and signs of an arthritis and can only be positively diagnosed by aspiration and bacteriological examination. Gonorrhœal infections as well as postpneumonic arthralgias have to be carefully excluded. The mortality is 65 per cent., largely as the result of the bacteriæmia, and the involvement of more vital organs and tissues, yet spontaneous recovery may occur even if there has been suppuration. Treatment should consist of immediate incision and drainage; the serous variety may be healed by aspiration, rest and compression. In 47 cases, 18 per cent. were below thirty and 70 per cent. between thirty and sixty years of age. As to arthritis with pneumonia in childhood, Bichat and Goepfert report 4 cases. In 2 the joint contained pneumococci; in 2 strep-

[1] *American Journal of the Medical Sciences*, July, 1902.

tococci and staphylococci. The former occurred in lobar, the latter in lobular, pneumonia. Two died; one recovered; in the third there was no note as to the termination. Perutz reports pneumonia in a child aged eleven months, in whom during a relapse, osteomyelitis of the left humerus developed; pneumococci were found in the pus. Among 55 cases of pneumococcus arthritis in adults Herzog found that pneumonia preceded in all but 4. In infants this occurred in 5 out of 8 cases, and in children in 2 out of 14.

As further complications of pneumonia the following conditions may be mentioned: *Thyroiditis* ending in suppuration has been reported by Honsell, and by Lion and Bensaude. This seems to occur as a sequel and to terminate favorably after incision and drainage. *Exophthalmic goitre* occurred 4 times in 2,440 collected cases. *Suppurative orchitis* with a lethal termination, after a pneumonic relapse, has been recorded by Prioleau. *Bed-sores* occurred in 3 among 1,552 collected cases. Preble noted 2 instances of *abscess* of the soft parts; in both pneumococci were found in the pus.

Pneumonia in Pregnancy.—*Frequency.*—Among 13,611 collected cases of pregnancy, there were 120 instances of pneumonia (0.8 per cent.). Jürgensen, in Vienna from 1858–70, among 1,842 cases of pregnancy found 2.3 per cent. had pneumonia. Grisolle saw 4 cases in ten years. Ransdell in the literature for the last twenty years could collect only 352 cases of coincident pregnancy and pneumonia. He believes that the rarity of the condition is to be explained by the lessened exposure of pregnant women to infection. Another reason lies in the fact that pneumonia is more common in males, especially in hospitals, from which most often statistics are gathered, and that the number of pregnant women in general hospitals is small. Ransdell found that of 190 patients in whom abortion occurred 70 died (36.7 per cent.), whereas of 118 who did not abort, only 12 died (10.7 per cent.). Abortion occurred in 58.8 per cent. of 352 cases. Of 144 patients with pneumonia in the first six months of pregnancy, 22.08 per cent. died, of those who aborted, 52.08 per cent. died. Of 164 cases in the last three months of pregnancy, 30.49 per cent. were fatal and 70.12 per cent. of those who aborted showed that the mortality as well as the frequency is higher during the latter part of gestation. Of 82 patients who died, 72 had aborted.

The relation of abortion to the day of pneumonia was:

Day of disease	1	2	3	4	5	6	7	8	9	10	11+
Number of abortions	7	18	27	12	16	10	8	3	5	2	13

Of 52 patients who aborted before the third day, 21 died (40.38 per cent.) and of 69 who aborted after the third day, 19 died (27.53 per cent.). These figures indicate that if abortion does not occur in the first few days, the prognosis is better. It will also be noted that the third day is the most common one upon which abortion occurs. The mortality according to age was as follows: below twenty-five years, 13.33 per cent., from twenty-five to thirty-five years, 23.2 per cent., and over thirty-five years, 22 per cent. Among 89 multiparæ, 8 died (20.11 per cent.), and of 13 primiparæ, 4 died (30.77 per cent.). As to the infantile mortality, of 142 infants in whom the age of viability had been reached, 58 died (40.84 per cent.). Cases of transplacental infection from mother to offspring have been reported by Thomer, Birch-Hirschfeld, Strachan, Marchant, Netter, Levy and others.

The mortality from pneumonia is increased by pregnancy. More than half of the patients abort and when this occurs the death-rate is much higher. It is also higher during the later months of pregnancy. When death ensues, it is usually induced by a diminution in the quantity of hæmoglobin, degeneration of the heart muscle, and overloading of the right heart after delivery.

Aufrecht has shown experimentally that in rabbits inoculatated with pure cultures of pneumococcus, abortion occurred as the result of endometritis and was often followed by peritonitis. It is reasonable to assume that an analogous process occurs in the human being, and that the high mortality after abortion results from a pneumococcic endometritis, having its origin in the organisms circulating in the mother's blood.

Menstruation in pneumonia has been reported by Griesinger. In one, normal menstruation appeared on the third day of the disease and continued uneventfully. In another it appeared on the fourth day of the disease, ten days earlier than it was due. Beginning with the onset of the flow there was an evening remission of the temperature, instead of an exacerbation, *which proved to be the beginning of* a slow defervescence by lysis.

Occurrence with Other Infectious Diseases.—Pneumonia may occur as a complication of any of the infectious fevers. In *measles* lobular is much more common than lobar pneumonia. Very often it may be impossible to definitely determine with which of the two forms we have to deal. It is probable that the acute infection of the respiratory tract which occurs in measles opens a pathway for the entrance of the pneumococcus. Collected statistics showed 5 cases of measles in 2,469 pneumonias (0.20 per cent.), but such figures possess only small value for obvious reasons. Incipient pneumonia may be very closely simulated by atelectasis. "If loud bronchial breathing is heard over a dull area, a diagnosis of pneumonia is established; if this sign is absent, pneumonia may exist or the case may be one of atelectasis only" (T. V. Jürgensen). If dulness clears up more or less on deep inspiration, atelectasis is the prominent lesion. What has been said regarding measles applies with equal truth to *scarlet fever*, in which pneumonia is a very serious complication, especially when it appears during the course of a scarlatinal nephritis. Under these circumstances it not rarely causes œdema of the lungs, pulmonary abscess or empyema. Among 550 cases of scarlet fever, Beatty found 5 cases of pneumonia. Croupous pneumonia in the course of an attack of *diphtheria* is less common than in either of the above-mentioned diseases.

The coincidence of croupous pneumonia and *influenza* is of considerable importance. Epidemics of the two diseases often occur simultaneously and when this happens the pneumonia is apt to run an atypical course, and be attended by a high mortality. Lobar pneumonia in influenza is nearly always produced by the pneumococcus, the Pfeiffer bacillus practically always causes the lobular variety. As to frequency, Birch-Hirschfeld in 108 cases of influenza found 11 cases of lobar pneumonia, Marchand in 5 cases of influenza pneumonia, found 3 of the lobar variety, Finkler observed typical influenza pneumonias among 45 cases of pneumonia in general. Krannhals among 1,687 cases of influenza, found 3.15 per cent. of typical lobar, 1.3 per cent. doubtful, and 2.2 per cent. of lobular pneumonia. He found the frequency of pneumonia increased five or six fold during the influenza epidemic. The disease chiefly affected individuals from twenty to fifty years of age and was most common in November and December.

The tendency to suppurative complications, both in and out of the lung, seemed to be increased. Not infrequently lobar pneumonia was found at autopsy in one lung, while the lobular variety occurred in the other.

When lobar pneumonia complicates influenza, chill at the time of onset is generally absent but repeated chilly sensations may occur. The skin is more apt to be moist and severe sweats may occur even during the fastigium. Termination by lysis is very frequent, and defervescence is followed by greater prostration. Rusty sputum is often absent and the character of the temperature irregular. Postmortem, contiguous areas of the diseased lung may be in quite different stages of hepatization. Finkler lays especial stress upon the fact that frequently the only physical sign pointing to pneumonia is the presence of percussion dulness over limited areas, no crepitant rales being audible at the beginning, although later on crepitus redux appears. Certainly influenza patients are very prone to develop pneumonia, a danger against which they should be warned.

Lobar pneumonia as a complication of *malaria* is practically always of pneumococcic origin. True pneumonia due to the plasmodium of malaria is unknown, although the parasites may be demonstrable in the pneumonic consolidation. This complication is attended with a high mortality; Ascoli places the figures at from 60 to 78 per cent. Such pneumonias are often latent and overlooked; they may be very closely simulated by pulmonary congestion which is seen in some cases of pernicious malaria. The last-named condition may be manifested by dulness, rales, cough, dyspnœa, bloody expectoration and even bronchial breathing. It generally occurs in the most dependent portions of the lungs. If true pneumonia is present the fever is apt to be continuous; if only congestion exists the temperature is of the intermittent variety characteristic of the malarial infection. Clinically, pneumonia complicating malaria assumes the asthenic type with prostration and marked nervous symptoms. Pneumonia is extremely frequent and fatal in individuals suffering from chronic malarial cachexia. Complications are frequent, especially delayed resolution, with subsequent fibroid induration, and also pneumococcus septicæmia.

In *typhus fever* lobar pneumonia is a very fatal complication, which is often unexpectedly discovered at autopsy.

Typhoid fever and pneumonia may occur coincidently or in rare instances the pulmonary consolidation may be due to the typhoid bacillus. Among 3,514 collected cases of pneumonia there were 56 cases of typhoid fever, 24 of which died (42.8 per cent.). In 522 autopsies in pneumonia, the lesions of typhoid fever were found in 17 and in 891 autopsies in typhoid fever, pneumonia was found in 42 (18 per cent.). In 98 autopsies on cases of typhoid fever, at the Pennsylvania Hospital, Philadelphia, G. C. Robinson found bronchopneumonia in 29, and lobar pneumonia in 13 cases. In 12 of the latter, cultures from the consolidated areas showed pneumococci in 4, and stained preparations in 3 other cases; the *B. typhosus* in 1; the rest were pyogenic infections.

Lobar pneumonia occurring as a complication of typhoid fever, is generally due to the pneumococcus, occasionally to the Friedländer organism or the typhoid bacillus. It appears most often during the latter part of the febrile period, rarely during convalescence or prolonged relapses. The onset is often insidious, a chill at the beginning being often absent. The course of the fever is not characteristic. The typhoid temperature may be somewhat

increased and when the two diseases terminate at about the same time, a rapid almost critical defervescence may be noted. The attention of the physician is usually called to the complication by increased pulse and respiratory rate or cyanosis. Pain, cough and expectoration are often absent; the latter when present is apt to be hemorrhagic. The course of an attack of pneumonia in typhoid fever is generally protracted, resolution is delayed, and consolidation often imperfect. Pneumonia as a complication of typhoid fever is probably more common than is generally supposed. The mortality of pneumonia is about doubled by the co-existence of typhoid fever. According to E. Kraus the presence of pneumonia in typhoid fever may prevent the occurrence of the Widal reaction, and may cause the same to disappear after it has once been present. Typhoid fever inhibits the development of leukocytosis in pneumonia.

Bressel has reported lobar pneumonia following *gonorrhœa*, with colorless expectoration, lysis after the eighth day, the fever having previously been high. Resolution was complete by the eighteenth day. The sputum showed intracellular diplococci, Gram negative, and blood cultures the gonococcus.

THE DIAGNOSIS OF LOBAR PNEUMONIA.

In typical cases probably no disease is more easy to diagnose than lobar pneumonia and such cases need not concern us here. Atypical cases may be confounded with acute tuberculous pneumonia, bronchopneumonia, especially in children, pulmonary congestion, pulmonary infarct, atelectasis, and most important of all, pleural effusions. In cases of central pneumonia the diagnosis may be in doubt for several days.

Aside from the physical signs, the symptoms and a study of the temperature chart are factors which often aid. When laboratory facilities are available, blood cultures are the most positive means of diagnosis. The absence of leukocytosis speaks strongly against pneumonia except in very mild or very toxic cases. A history of chill at onset, especially if followed by chest pain, pyrexia, rusty sputum, or herpes, often settles the diagnosis. The mode of onset, the course of the fever, the pain in the chest, the cough, the peculiar expectoration, the dyspnœa, the abnormal pulse-respiration ratio, the peculiar character of the breathing—all of these have to be borne in mind in making a diagnosis in cases of obscure character. It must also be remembered that pneumonia is a disease of protean manifestations and that it often presents abnormalities of type; this is especially the case at the extremes of life, in drunkards, and in chronic disease. Whenever we have to deal with fever of uncertain origin, the lungs must be repeatedly and carefully examined. It is only by exercising unceasing vigilance that we can avoid having unsuspected pneumonias brought to our attention by the consultant or at autopsy. We should be particularly on our guard when we have to deal with a case of *influenza*, not only because this disease is frequently complicated by pneumonia, but also because when these two conditions go hand in hand the clinical picture of pneumonia is apt to be very atypical. When the possibility of pleural effusion arises it may be promptly settled by an exploratory puncture, although we must bear in mind that there may also be an underlying pneumonia. Subdiaphragmatic abscess may be excluded by the fluorescope. The positive determination of a tuberculous

process is often impossible until during convalescence, when delayed resolution, tubercle bacilli, night sweats, or evidences of cavity formation may clear up the condition. It must be borne in mind that acute exacerbations of tuberculous processes which are too often considered as influenza with bronchopneumonia, may resolve to quite a remarkable extent. In such cases the true state of affairs may be learned by the use of tuberculin after the fever has subsided. Cavity formation does of course not necessarily indicate tuberculosis; it may result from gangrene. In this connection the previous history of the patient is of great importance.

When the patient is not seen at the beginning, it is often extremely difficult to distinguish between pneumonia and *pleural effusion*. In the former disease the temperature is generally higher, leukocytosis more marked, and the sputum rusty, but it is not in the typical cases that doubt arises. Theoretically the physical signs of the two diseases should be quite different, but practically one finds cases of pleural effusion in which vocal fremitus, vocal resonance and even bronchial breathing are present, or the breath sounds are only slightly modified. On the other hand in some cases of pneumonia we find only partial suppression of the vesicular murmur or feeble distant tubular breathing; increased fremitus and resonance are by no means always present. In both conditions we may have Skodaic resonance over the upper lobe, accompanied by exaggerated, harsh breath sounds. It may easily be seen that a differential diagnosis cannot be made upon any one symptom or sign, but upon a consideration of the whole picture. In doubtful cases the presence of pneumococci in the central parts of washed sputum often settles the diagnosis. Movable dulness does not exclude an underlying pneumonia, nor does the demonstration of liquid in the pleural cavity by means of exploratory puncture, although both of these conditions may throw much light upon the question. Bronchial breathing may occur in pleural effusion as the result of pulmonary compression by the exudate, but in such cases it is usually best heard, sometimes only heard, over the middle or upper parts of the lung, and not at the base. In cases in which dulness appears suddenly and remains limited to the lower lobe the process is generally a pneumonic one. In making an exploratory puncture one should use a needle sufficiently long and of not too small a calibre, introducing it in the area of greatest dulness. Any signs of displacement of organs such as the heart, the liver or the spleen, speak in favor of pleural effusion, but unfortunately such conditions may be absent. It should also be borne in mind that the heart may be displaced by consolidation of the lungs.

In pneumonia the affected side moves less than the sound side, but not to the same degree as in effusion. In percussing over an effusion, there is a greater degree of dulness and the sense of resistance is much more marked. In pneumonia the area of dulness corresponds to the lobes of the lung, in pleural effusion the upper level of dulness follows an S-shaped curve, with the highest point in the axilla. In pleural effusion it is generally possible to demonstrate Grocco's sign—a triangular area of dulness over the opposite lung posteriorly, the apex being situated at the spinal column, at a height varying with the amount of the exudate, and the base at the lower limits of the pleural cavity.

Interlobar empyema may give signs and symptoms practically identical with those of pulmonary consolidation, being most often confused with delayed resolution or tuberculous infiltration. The reappearance of fever,

malaise, weakness, leukocytosis and pain after the disappearance of these following the crisis, should make us search very carefully for this condition. In these cases the exploratory needle and the *x*-rays are most useful. If no evidence of pus is found by the needle in the area of greatest dulness, we may at times demonstrate its presence by following up the neighboring regions which correspond to the septa of the individual lobes of the lung.

The differential diagnosis between incipient lobar pneumonia and acute *abdominal inflammations*, especially appendicitis, has been considered.

In the early stages it may be difficult to differentiate *typhoid fever* and *meningitis* from atypical forms of pneumonia.

Secondary pneumonias occurring in the course of other diseases are often overlooked. Even when suspected and sought for, the physical signs are not rarely of equivocal import, it being impossible to determine positively whether we are dealing with an hypostatic congestion, œdema, infarct, a central pneumonia or a bronchopneumonia. In all doubtful cases a disturbance of the normal respiration-pulse ratio—1 to 4 in adults—is very suggestive. In such cases every part of the chest should be very carefully examined, particular attention being given to the auscultatory phenomena high up in the axilla, above and below the clavicles, and under the scapulæ. No matter how carefully we make our examinations, we must expect from time to time to make a diagnosis of pneumonia without any positive physical signs. In children it occasionally happens that these do not become manifest until after the crisis.

THE PROGNOSIS OF LOBAR PNEUMONIA.

Wells has collected from the literature, 465,400 cases of pneumonia with 94,826 deaths, a mortality of 20.4 per cent. Among the older writers we find frequent statements to the effect that the mortality from pneumonia is small. Thus Trousseau says, "Generally speaking there is a tendency to spontaneous recovery." Flint states, "Recovery is not only the rule, but the exceptions are exceedingly infrequent." Bennett even goes so far as to say that in uncomplicated cases, properly treated the mortality should be practically *nil*. Gerhardt believed that in private practice the mortality should range between 2 or 3 per cent. There are to be found, however, numerous statements to the effect that pneumonia should be regarded as a very fatal disease (Loomis, Sturges, Drake, Watson, Copland, etc.). At present nearly everyone concurs in the belief that pneumonia is one of the most fatal acute diseases. Strümpell stands alone in his opinion that "pneumonia belongs to the benignant infectious diseases" (Wells).

It matters little whither we turn for our statistics, we are apt to find a mortality ranging from 20 to 25 per cent., taking any large series of cases as they come. Articles are constantly appearing, written by the enthusiastic advocates of certain lines of treatment, proclaiming a greatly diminished death-rate, supposedly the result of therapeutic success, but the mortality from pneumonia holds its own, unabated, in much the same proportion as that which our predecessors saw. Thus among 43,455 cases collected by the writers, 21.06 per cent. died.

According to the United States census for 1900 the death-rate from pneumonia per 100,000 of the population was highest in the registration cities of

the registration states (233.1), lowest in the rural districts (135.9). It was much higher among the colored (349), than among the whites (184.8); higher for foreign whites (209.8) than native whites (176.9); also higher for native whites having one or both parents foreign (212.2) than those having native parents (155). There has been a slight increase of the death-rate in the cities since the census of 1890, and a decrease in the rural districts. "The death-rate from pneumonia was excessively high among those whose mothers were born in Italy (479.8), particularly in the cities (561.4). Among those whose mothers were born in other countries the rates were highest among those whose mothers were born in Ireland (257.5); in Hungary and Bohemia (206.6). The rate was lower for the children of mothers born in the United States (142.8) than in any other class except those whose mothers were born in Canada (136.2)."

"The death-rates from pneumonia were highest among those under fifteen years of age (277.1), and at sixty-five years of age and over (805.4). At each age under sixty-five years the mortality from this disease was higher in males than in females; but at the age of sixty-five years and over the female mortality exceeded that of the males." In comparison with the figures of 1890, those of the 1900 census show a decreased mortality for those under sixty-five years of age; and an increase for those above this age. As regards the mortality according to *sex*, the statistics collected by the writers of 33,351 cases in males showed 6,449 deaths (19.3 per cent.) and among 12,927 cases in females, 3,431 deaths (26.9 per cent.). The total of 46,278 cases gave 21.1 per cent. mortality.

Age.—The high mortality from pneumonia, especially in the aged and in those afflicted with chronic disease, is largely due to complications. This is well exemplified in Ashton and Landis' series of 991 cases from the Philadelphia General Hospital, in which the general mortality was 53 per cent. If the disease could be shorn of its complications, the death-rate would be reduced more than one-half. The vast majority of the senile cases end in death, owing to the fact that the heart is no longer able to cope with the pulmonary obstruction, the kidneys and skin to eliminate the toxin, or the central nervous system to endure against the toxæmia.

Complications.—The mortality in relation to complications in collected cases is as follows:

Complications.	Cases.	Mortality.
Pleural effusion	700	20.29
Empyema	74	39.19
Acute endocarditis	36	72.22
Chronic endocarditis	114	32.46
Acute pericarditis	125	64.00
Acute meningitis	33	93.93
Jaundice	344	15.7
Cirrhosis of liver	5	100.00
Peritonitis	7	100.00
Acute nephritis	116	65.52
Chronic nephritis	182	68.29
Acute arthritis	52	61.0
Emphysema	48	47.9
Pulmonary tuberculosis	215	57.9
Pregnancy	466	30.0
Hemiplegia	105	21.8

Repeated attacks of pneumonia seem to decrease the virulence. Baeck, Morhart, Pöhlmann and Stoertz all found a lower mortality among those

individuals who had had previous attacks. Rychner's general mortality in 616 cases was 25.7 per cent.; whereas among those who had already suffered from the disease it was 22.7 per cent.; and among those who had had more than one attack it was 18 per cent.

Site.—The influence of the *site and extent of the lesions,* is shown in the following tabulations based upon 4,062 cases, reported by Townsend and Coolidge, Sears and Larrabee, Aufrecht, Meyers, and Norris, as collected by Preble.

	Cases.	Deaths.	Per Cent.
Right upper	448	90	20.0
Right middle	95	14	14.7
Right lower	1,129	195	17.2
Right lung	336	141	42.0
Left upper	185	34	18.9
Left lower	1,002	145	14.4
Left lung	309	84	27.1
Bilobar	251	91	36.2
Bilateral	307	110	35.5

The mortality according to the involvement (Sears and Larrabee) was:

	Cases.	Per Cent.
One lobe	590	31
Two lobes	233	38.2
Three lobes	99	59
Four lobes	8	62.5
Five lobes	1	100
Double pneumonia	134	42.5

The *mortality* according to the *site of involvement* in the series collected by the writers was: of 1,849 right-sided, 365 or 19.2 per cent. died; of 1,129 left-sided, 189 or 16.7 per cent. died; and of 601 bilateral, 218 or 36.3 per cent. died.

Temperature.—The effect of different *degrees of temperature and the pulse and respiration rate upon the mortality* is exemplified by Preble as follows. It will be noted that extremes of temperature are to be feared; low or subnormal temperature often indicates lack of reactive power on the part of the patient, whereas hyperpyrexia often goes hand in hand with a toxæmia which is overwhelming.

Temperature and Mortality.

	Cases.	Deaths.	Percentage.
Under 100°	17	6	35.2
102°	220	52	23.1
103°	302	83	27.4
104°	408	109	26.7
105°	386	99	26
106°	148	45	30.5
Over 106°	34	23	68

Pulse and Mortality.

	Cases.	Deaths.	Percentage.
Under 100°	57	2	3.5
110°	123	7	5.7
120°	142	18	12.6
130°	288	62	21.5
140°	143	68	47
150°	125	74	59
Above 150°	83	64	77

Respiration and Mortality.

	Cases.	Deaths.	Percentage.
Under 30	77	6	7.7
40	257	36	14
50	384	116	30.2
60	123	62	50.4
70	98	61	62.2
Above 70	23	14	65.6

To a certain extent the pulse rate may act as a prognostic indication. Chatard in the Johns Hopkins Hospital found in cases with a pulse rate below 125, a mortality of 14.9 per cent., a condition which occurred in one-half of the cases. With a pulse rate above 125 the mortality was 49.4 per cent.

Race.—W. Kolle, who studied an epidemic of pneumonia among the negroes at Kimberly, South Africa, found in over 1,000 cases a mortality of 60 to 70 per cent. According to the United States census report of 1900, the mortality from pneumonia among the negroes is 349 per 100,000 population while that of the whites is only 184.8. The high mortality in the negro is probably due to the same causes which have been considered under susceptibility. In addition we have the fact that in this country, at least, many of those classed as negroes are mulattoes, a stock which lacks resistance, and falls an easy prey to disease.

Alcoholism.—The role of alcohol as a predisposing cause has already been noted. It has long been known that habitual drunkards have a very slim chance of recovery when attacked by pneumonia and it is noted also that the mortality among moderate drinkers is higher than among total abstainers. This fact has long been known to life insurance companies, as holding good for many diseases other than pneumonia. Delirium tremens complicating pneumonia is very frequently fatal. The statistics of a number of observers are collected in the following table:

Mortality.

	Total Abstainers. Per Cent.	Moderate Drinkers. Per Cent.	Intemperates. Per Cent.
Collective Investigation Report	10.4	17.4	42.8
H. H. Smith	20.0	32.0	70.0
Sears and Larrabee	25.0	26.7	45.5
Huss			25.0
Hadden, Mackenzie and Ord			37.0
Townsend and Collidge	Combined	15.0	41.0
Norris	Combined	25.0	96.0
Aufrecht	Combined	24	45.3

Altitude.—Hoagland collected statistics of 6,116 cases in cities approximately at the sea level and found a general mortality of 26.8 per cent. In 709 cases occurring in cities at an average altitude of 6,580 feet the mortality was 22.1 per cent. He believes that there is no doubt that a line of demarcation exists as we ascend in altitude at which pneumonia is more fatal than at sea level, but statistics must be obtained from other countries and at an altitude greater than 7,000 feet in order that we may reach any definite conclusions.

Roberts from observations upon his own cases at altitudes of 200 to 300 and 3,000 to 4,000 feet, had a slightly lower mortality in the latter. He found

that heart complications were more frequent in the mountains, gastric and bowel troubles in the lowlands. Goodman in a study of 101 cases treated at the American Hospital at Mexico City found a mortality of 39.8 per cent. The disease was more frequent before the rainy season, and decreased during the rains and directly afterward. Connell agrees with Hoagland in a study of 261 cases at Leadville, Colorado, with a mortality 26.4 per cent., and holds that it has been practically disproved that high altitudes increase the death-rate of pneumonia. Kieffer states that among 127 cases at Fort D. A. Russell, Wyoming, at an altitude of 6,195 feet, during the last thirty-eight years, there were 20 deaths (15.74 per cent.). From 1868 to 1903 there was a mortality of 14.63 per cent. at Fort Russell, whereas in the whole U. S. Army during the same period there was a mortality of 15.61 per cent. Brewer, who has made a study of the subject based upon various United States Army statistics, arrives at practically the same conclusions.

CHAPTER XXIII.

THE PROPHYLAXIS AND TREATMENT OF LOBAR PNEUMONIA.

By JOHN H. MUSSER, M. D.,

AND

GEORGE WILLIAM NORRIS, M. D.

THE PROPHYLAXIS OF LOBAR PNEUMONIA.

The infectious agent is transmitted from the diseased to the healthy individual chiefly through the sputum but as the pneumococcus is found in the nasal and oral cavities of apparently healthy people, a dissemination from this source is also possible. Whether the organisms hitherto so considered shall prove to be identical, whether different strains of the same organism may develop essentially different characteristics, and, if so, through just what chemical or biological conditions their virulence may be diminished or enhanced, are momentous questions which the bacteriologist must decide. The evidence points to the fact that the problem is an extremely complex one, and that a large number of factors may affect the virulence of the organism and influence the resistance of the individual. It would seem that certain people are predisposed to the disease, but in what this diminished resistance consists we are unable to say.

It is unlikely that the increased prevalence of pneumonia is due to any general deterioration of resistive power, although it is believed that the growing frequency of cardiovascular degenerations plays an important role. This would not, however, explain the increase of pneumonia in children and young adults. Until these questions are more definitely settled from a bacteriological standpoint it would be useless to adopt the extreme measures of placarding houses and instituting a state of quarantine, advocated by some enthusiasts. On the other hand, all reasonable care should be exercised in the disinfection of sputum.

F. C. Woods, who has made a careful study of the viability of the pneumococcus has arrived at the following conclusions:

A. The life of the pneumococcus in moist sputum is of considerable duration, the average period being less than two weeks unless the material is exposed to direct sunlight. But, as such sputum does not give off bacteria even when exposed to strong currents of air, it may be considered as innocuous except to persons handling clothes, bedding, etc., which have recently been contaminated. Under ordinary conditions this sputum dries in the course of a few hours or days. The dried masses retain their virulence for a long time and if deposited on the floor or on bedding may be powdered mechanically, and sweeping, dusting, or brushing the contaminated articles will distribute pneumococci in the air. Fortunately, the organisms do not

remain long in suspension and die rapidly under the action of light and desiccation. In sunlight or diffuse daylight the bacteria in such powder die within an hour, and in about four hours if kept in the dark. The danger from infected sputum may be avoided by ample illumination and ventilation of the sick-room in order to destroy or dilute the bacteria and by the avoidance of dry sweeping or dusting. Articles which may be contaminated and which cannot be cleaned by cloths dampened with a suitable disinfectant should be removed from the patient's vicinity.

B. When a person suffering from a pneumococcus infection coughs, sneezes, expectorates or talks, particles of sputum or saliva are expelled from the mouth, which may contain virulent pneumococci. Such particles remain suspended in the air for a number of hours if the ventilation of the room is not good. They may be inhaled by persons in the vicinity or deposited upon various articles in the room. Whether suspended in the air or dried on surrounding objects, they become harmless in a very short time, about an hour and a half being the extreme limit, while many of the pneumococci in the spray perish in a few minutes, especially if exposed to strong light.

The risk of infection from the pneumococcus is largely confined to those in direct contact with the patient.

Pneumococci have been isolated from the throats of 50 out of 80 normal individuals, from 66 out of 74 cases of lobar and lobular pneumonia, from 10 out of 15 common "colds," and from 14 out of 31 cases of miscellaneous disease. It is also probable that the virulence of the pneumococcus is somewhat higher in pneumonia than in "normal" cases, although this is a very difficult matter to determine. Wells was able to demonstrate the pneumococcus in the respiratory passages, chiefly the throat, of 62 out of 135 individuals examined (45 per cent). Certain other findings of the Medical Commission for the Investigation of Acute Respiratory Diseases, should be noted; namely: (*a*) while a small number of individuals constantly harbor virulent strains of the pneumococci in their mouths, the majority of people do so only from time to time. (*b*) Individuals who come in contact with pneumonia patients harbor the microörganism in much greater proportions than those not so exposed. (*c*) Infection may be acquired from droplet infection, from dried sputum, and from actual contact with utensils which have been used by pneumonia patients. (*d*) Patients convalescent from pneumonia may carry virulent organisms in their respiratory passages for weeks or even months. (*e*) It is probable that infection may be acquired from some cases of ordinary "cold."

The disinfection of sputum is best accomplished by keeping a strong solution of lye or sodium hydrate in the sputum cup, the use of which should be enforced. The addition of bichloride of mercury, carbolic acid, and other disinfectants to sputum simply produces a coagulation of the peripheral mucus while the central part of the coagulum is protected. When isolation is possible, it should be carried out, especially in hospital wards and in rooms generally occupied by more than one member of a family. Patients enfeebled by age, renal and cardiovascular lesions or acute illnesses such as typhoid fever and influenza should be kept from contact with, or even proximity to a patient with pneumonia. When association is unavoidable the bed should be screened, a procedure which would tend to minimize general aërial dissemination of microörganisms expelled in coughing. Those nursing pneumonia patients should be warned against needless handling of, or proximity

to the patient, and of touching their own face without careful disinfection of the hands. Aged and debilitated individuals and those who have once been attacked by pneumonia should preferably not be selected as nurses.

In regard to the general combatting of the disease, something may be hoped for through the education of the public. It should be common knowledge that anything which tends to reduce the vitality—dissipation, loss of sleep, overwork, overworry, underfeeding, alcoholism, etc.—predisposes to an attack of pneumonia. Further, that exposure to cold, draughts, or any chilling influence when overheated and perspiring, and especially when physically exhausted, directly invites infection. The foregoing statements by no means indicate coddling, overclothing or bad ventilation. It should be equally understood that the habituation of the body to cold air or water, when not carried to extremes, and when followed by a vigorous systemic reaction, is highly beneficial, as is also thorough ventilation and the habit of sleeping with open windows.

The duties of the municipal government should consist (*a*) in helping to disseminate knowledge of the above-mentioned character, (*b*) in enforcing regulations forbidding expectoration in public places, especially within doors, (*c*) in proper cleaning of the streets, a procedure which should always be preceded by thorough sprinkling, and performed only at night, (*d*) in systematically disinfecting rooms in which patients with pneumonia have been lodged.

It is to be hoped that the future may bring forth some specific prophylactic measure, in the nature of a serum or an inoculation. Such a thought is not new, as the following quotation shows: "The Moors and the Pouls of Senegambia have a custom whose origin is lost in the obscurity of antiquity, which consists in the inoculation of their cattle with the virus of epizoötic pleuropneumonia." A knife is thrust into the lungs of an animal dead of the disease and then plunged subcutaneously into a healthy animal in the supranasal region. Experience has demonstrated a protective result (De Rochebrune, 1885).

THE TREATMENT OF LOBAR PNEUMONIA.

The historical consideration of the treatment of pneumonia offers a gloomy retrospect, the sombre hue of which is not much lightened by the contemplation of the present. Ever since the days of antiquity, pneumonia has been observed and studied, while one method of treatment after another has been vaunted with enthusiasm, only to be abandoned in despair; the disease meanwhile pursuing the even tenor of its way, with scant respect for the methods employed against it.

Hippocrates treated pneumonia by laxatives, expectorants, cups or the actual cautery and with baths on the fourth and seventh days, and oil inunctions on the fifth and sixth. The principal food administered was of fatty and saline character. For some cases elaterium was recommended. Galen, in 230 A. D., advocated venesection, a practice which was strenuously opposed by Epistratus. Laennec stated that "in every case the more feeble the pulse, the less the indication for blood letting." In 1830, Dewees stated that nearly all writers agree that the proper treatment of pneumonia should consist in: (1) Venesection—local and general, (2) purges, (3) blisters, (4)

alteratives, (5) antimony, and (6) tonics. Nearly all of these remedies have from time to time been employed in heroic doses; thus, we find Marshall Hall bleeding his patients to the point of syncope.

Quinine, aconite and veratrum viride were much in vogue about 1860. In 1880, especially in Germany, cold, in the form of baths, compresses or packs, was much used. About 1899 various drugs with germicidal qualities were extensively employed—creosote, chloroform, salicylic acid, etc. Recently various serums have been tried, and although their employment is based upon the most natural and therefore the most logical grounds, their use, certainly so far as curative effect is concerned, has been valueless.

Undoubtedly one of the most salutory events, so far as treatment is concerned, was brought about by the Vienna school of therapeutic nihilism, inspired by Skoda. As the result of its doctrines the fact was thoroughly demonstrated that pneumonia is a self-limited disease, with a natural tendency toward recovery, and that Nature can do more for the patient than the routine application of any one method of treatment indiscriminately applied. Previous to this time it had been the custom to treat pneumonia with large doses of antimony, aconite and other powerful depressants.

Specific Treatment.—*Mercury*, in the form of calomel, has been very extensively employed in pneumonia for its supposed "antiphlogistic" effects, sometimes to the point of salivation, or in enormous single doses, ranging from 20 to 60 grains a day. It has also been used with opium, the idea being that it would thus be absorbed and exercise an antiseptic action. By some, its use in the early stages has been credited with aborting the pneumonia. The *iodides* have been employed in over 250 cases by Altshul with a mortality of only 1 per cent. Potassium iodide was given in rapidly increasing doses up to 3,000 grains daily. The drug is said to have been well borne. Digitalis has had many enthusiastic supporters, chiefly in Italy. Its employment was based upon the fact that very minute quantities of digitalis would prevent the growth of the pneumococcus in vitro. It has been given in doses of from 4 to 5 grams daily. Capuano believed that this drug exercised a beneficial action through the production of leukocytosis.

Veratrum viride was at one time enthusiastically endorsed by no less an authority than H. C. Wood, especially in the early stages, the theory being that the patient was "bled into his own vessels," and that in this way engorgement of the lung was prevented and sometimes an attack of pneumonia aborted. With the present conception of pneumonia it is hardly credible that the disease may be aborted by any physical means. *Chloroform* inhalations have been used extensively and for prolonged periods of time by Clemens of Frankfort, based upon a supposed sedative, antiseptic, anticoagulative action, as well as for the relief of pain. This author states that he has treated every case of pneumonia occurring in his practice during the last forty years by this method—without a death! *Quinine* too has been very extensively employed, and still has some strong advocates. The theory of its use seems to be that of a germicide and antipyretic. This treatment was employed by Petresco in 1891 and has lately been revived by Galbraith and others. The latter gives from 30 to 120 grains of quinine daily, with tincture of ferric chloride. The *salicylates* have also been much vaunted. Liegal treated 72 cases of pneumonia in miners, ranging in age from sixteen to seventy-four years, in doses of not less than 8 grams daily. All of his patients recovered. *Creosote*, either pure or in form of the carbonate, has been

considerably used of late. Van Zandt has collected 1,130 cases treated by this method with a death-rate of 4.9 per cent. Creosote has also been administered by inhalation and by rectal injections. Scott and Montgomery treated 67 patients at the Pennsylvania Hospital, Philadelphia, with carbonate of creosote, 10 to 15 minims every two or three hours, with a mortality of 14.9 per cent. Intravenous injections of colloidal silver have been used by Thiroloix.

An entirely new departure in treatment has been made by Albert Robin, based on the fact that small solutions of certain metals—platinum, gold, silver, palladium—are apparently capable of influencing the chemical reactions of elementary nutrition. This action consists, so far as known, of a stimulation of the hydrating and oxido-reducing phenomena correlative to a certain number of vital acts. In pneumonia with a fatal ending, the co-efficient of nitrogenous utilization falls on the average to between 68 and 73 per cent., and the output of urea is more or less decreased. In patients who recover, the co-efficient varies from 77 to 82 per cent. at the height of the attack. It rises, as does urea also, a little while before the thermic defervescence, to increase still further later on. Since at the same time the oxygen consumed diminishes, the respiratory quotient is increased. The crisis occurs coincidently with the exaggeration of the hydrating and oxydo-reducing acts. The similarity which exists between the clinical phenomena at the crisis and those determined by the metallic ferments suggested that the former might be aided by the latter, the metallic ferments increasing the normal means of defense. Robin treated 14 patients in this manner, giving hypodermic injections representing the active principle of the metals, and got chemically very distinct results: increase of urea, increase in the co-efficient of nitrogen utilization, increase of uric acid, and free elimination of indoxyl. Thirteen out of 14 recovered.

The treatment of pneumonia by *serumtherapy* has been unproductive of beneficial results sufficient to warrant its recommendation. Anders has collected 535 cases treated by this method—61 cases by diphtheritic, and 474 by antipneumococcic serum—with 85 deaths, a mortality of 18.3 per cent. Since the publication of Ander's article, Paessler, Winkelmann, and also Leichtenstern, have reported on 24, 16, and 4 cases, respectively, treated with Roemer's serum with a joint death-rate of 25 per cent. Tartaro has treated 25 cases with Pane's serum, 2 ending fatally. The reports of individual observers have in some cases been very laudatory, but when a large number of cases is reviewed the results are unsatisfactory. It should be stated, however, that some physicians who have used the serum, although admitting that it had no direct curative effect, were nevertheless impressed with the fact that the patient's general condition, at least so far as comfort was concerned, was materially improved.

The reasons which may account for the failure of this most rational form of therapy are several. To begin with, as Welch has pointed out, the present stage of progress does not hold out much hope for a protective antitoxin, owing to the low vitality of the pneumococcus in artificial inoculation, and, further, that there is absolutely nothing which can be termed specific in pneumonia. What is clinically recognized as lobar pneumonia may be caused by a variety of different organisms or by mixed infections. Leaving the Friedländer bacillus, the Eberth bacillus and the pneumococcus out of the question, the researches of the Pneumonia Commission have shown

quite clearly that there are at least two types of organisms which bear very close, though as yet not definitely determined, relations to the pneumococcus, namely: a diplococcus very similar to the pneumococcus, which does, however, not ferment inulin, and the *Streptococcus mucosus capsulatus*, an organism more nearly akin to the pneumococcus than to the *Streptococcus pyogenes*.

The vulnerability of the pneumococcus is well known. In view of this fact it would at first sight seem reasonable to attempt to check its growth by various antiseptics, administered either by inhalation, by mouth, by hypodermic injection, or by inunction. All of these have been tried with a vast array of drugs, and sooner or later they have been found wanting. Several facts are frequently overlooked by the enthusiastic employers of different remedies, which it is worth while to briefly point out.

First: pneumonia is a general systemic infection with local manifestations in the lung. In many cases the pulmonary lesion is only secondary both from the standpoint of infection and in its importance in producing a fatal termination. Second: pneumonia is a definitely self-limited disease, just as typhoid fever, which may occur in an abortive form by reason of decreased virulence on the part of the organism or increased resistance on the part of the individual. A specific effect might be very readily attributed to the action of a certain remedy which had been administered. Third: the mortality from pneumonia varies more or less in different years, epidemics, and localities. For obvious reasons, it varies greatly in small series of cases treated by the same methods, so that the individual observer is very apt to draw false conclusions. Fourth: pneumonia is often due to mixed infection, or to entirely different varieties of organisms, conditions which we are at present rarely able to positively or promptly determine. This factor probably in part accounts for the very diverse conclusions which have been arrived at by different observers who have employed different kinds of therapy.

The review of the methods of treatment of pneumonia might be extended almost indefinitely. The brilliant results of specific remedies lauded by some fail to materialize when the same remedies are tried by others. It is to be regretted that there seems to be a tendency from time to time to take up various old, well-tried, forgotten, and useless forms of medication.

We have at present no specific for pneumonia, and such a specific must come through the development of serumtherapy. Each claimant for a specific treatment can, nevertheless, produce statistics to support his statements, providing the critic does not insist that the following considerations must qualify any presumed facts:

1. A number large enough to exclude the personal equation and other qualifying features must be analyzed.

2. The age, sex, social circumstances and habits; the environment, character of epidemic, season of year, and circumstances of the life-history of the host as well as of the pneumococcus, and many other details, must be constant features in the groups of cases arranged for comparison. The pneumococcus may at any time be virulent, at another innocuous, or the host susceptible or relatively immune. Neither the host nor the organism are constant factors. Thus far in all literature there are no such comprehensive analyses. The thoughtful physician is compelled, therefore, to put aside all such vaunted specifics and subscribe to lines of treatment based upon physiological principles, derived from our knowledge of the action of the organism and the reaction of the host.

The action of the organism is that of an invasion or infection of the host inducing a general infection, a local inflammation, and a secondary toxæmia. A favorable reaction of the host is seen in the ability to take care of the inflammation by physiological means, and to neutralize, eliminate, or withstand the effect of the toxins. As to the organism, after invasion or infection has taken place but little can be done by the therapeutist, save to perhaps limit the inflammation or prevent reinfection. To secure these we must lessen congestions which become points of lessened resistance and hence vulnerable to further invasions, we must ward off other microörganisms to prevent mixed infections, and we must prevent reinfections of the pneumococcus.

As to the host, we must aid every line of defense provided by nature. The nervous system, the circulation, the digestive apparatus and the secretory organs must be carefully studied and their functional activity looked to. The aged, the debilitated, the sufferer from organic disease, should thus receive the help their enfeebled powers demand. In short, any attempt to defeat the inroads must be attained by a careful study of the host. It is on the patient, therefore, that most reliance must be placed for recovery and hence his resistance must be fortified and his powers of elimination aided. Fortunately many individuals evince enough power of defense, as manifested by good resistance and sufficient elimination. We know that death ensues in uncomplicated cases either from an overwhelming extent of the inflammation or from the toxæmia. These factors serve, therefore, as the indications for treatment, and are in truth our conception of the morbid process which we have to combat. To do this successfully we must play with Nature's cards.

General Considerations.—When we are dealing with pneumonia, the scenes change rapidly and the passage of an hour or two may present an entirely different picture. The obvious lesson of this is that pneumonia patients should be watched carefully and seen by the attending physician at frequent intervals, especially during the latter part of the disease when judicious and well-timed medication may tide the patient over the crisis to recovery. Furthermore, the physician should always remember that there is no routine treatment, that each patient must be a law unto himself, and, finally, that it is the individual who needs treatment, not the disease. When clamorous relatives insist that something be done, it is far better to give a placebo than to risk the administration of any remedy whose physiological action is not clearly understood and whose employment is not definitely indicated. As Hare has very aptly stated, the physician "must be the watchman all the time, and the therapeutist only when treatment is actually needed." "All patients may be divided into three groups, those doomed to death by the malignancy of the infection, those that are but slightly ill by reason of mild infection, and those who are between the two extremes and need careful medical aid to accomplish recovery." For the first group no known treatment avails, for the second none is needed, but in the third therapeutics finds a legitimate and fertile field.

The Inflammation.—The inflammation is the result of an infection, liable to increase in extent if the cause persists, atria of infection prevail, or local and general resistance falls below normal. Such local resistance is lessened if congestions are present, whether from cardiac, renal (toxic), or traumatic causes as we see in traumatic pneumonias. General resistance,

on the other hand, is lowered by unhygienic conditions, by antecedent depressing influences, as disease or alcohol, and by the action of the toxin. We must consider the patient as an infected subject liable to reinfection from the same organism derived from without or resident within the mouth or fauces.

The patient should be scrupulously cleansed and then kept clean. The assailable mucous membranes should be cleaned and all abrasions sealed. The eyes, the nose and throat, and above all the mouth should have thorough and repeated cleansing with mild antiseptic lotions. The laryngitis, tracheitis and bronchitis which frequently precede or accompany the infection should be treated by cold compresses and other hydrotherapeutic measures, by local counter-irritation, by the inhalation of proper medicated sprays or vapors and by the usual remedies if they do not conflict with or replace medication that is necessary for the major infection. The discharges should be disinfected and destroyed at once.

Adequate *ventilation* of the sick-room is of the greatest importance. There is absolutely no danger of the patient catching cold, even when the windows are wide open. Thorough ventilation is of especial importance if the room is small, if it is occupied by several people, or if there is a stove or light burning in it. In addition to being well-aired the bedroom should have as much sunlight as is compatible with the comfort of the patient. The temperature should never be above 65° F., visitors and unnecessary attendants should be excluded, the use of the bed-pan enforced, and preferably a single bed should be chosen.

Aërotherapy.—We owe to Northrup the most recent energetic and convincing statements of the value of this procedure. Fresh air stimulates the heart and respiration. It supplies requisite oxygen, relieves "air hunger," promotes sleep, quiets restlessness and promotes digestion. As Jürgensen long since pointed out "fever patients cannot catch cold." Franklin wrote, "Colds, so-called, are utterly independent of either wet or cold."

Method.—If possible choose a sunny room, have the windows wide open, or the sashes taken out, regardless of weather or temperature. If there is dust or snow replace the window panes by cheese-cloth screens. The temperature of the room should preferably be below 65° F. Supply extra wraps for the nurses. Hot foot baths, followed by friction, are very beneficial. These and rectal injections can easily be given under the bedclothes. The patient's arms may be left outside the covers. Northrup pointedly says, "Do not make the patient breathe five times when three will accomplish the same effect. Give him air, fresh air, in unlimited amounts and constantly."

In the past few years excellent results have been obtained by treating the patients in tents or on protected verandas. But little medication was given. It does not seem possible that any one should cavil as to the advantages of such treatment; but it is necessary, before these plans can be adopted, to educate an unwilling public.

The *patient should wear* light woolen undergarments to prevent sudden changes of temperature and should never be clothed heavily enough to produce discomfort or profuse perspiration. Woolen and cotton jackets are still used by a few practitioners. The jacket poultice is, fortunately for the patient, a thing of the past, although of late it has been supplanted to a slight extent by a somewhat similar procedure—that of applying various forms of pastes to the chest. The only advantage which such forms of treatment

possess lies in their relief of pain and this can be much more satisfactorily accomplished by other means.

It is needless to say that all means which might disturb physiological processes must be guarded against. Improper feeding, undue exertion, excitement, and other disturbing influences, must be corrected. When it is recalled that a large proportion of pulmonary pneumococcus infections are attended by infections of the colon, the influence of diet can be appreciated.

Blood Letting, Cupping, External Applications.—With the intention of controlling the extent of the inflammation, one of the measures above suggested may be employed. If the patient is robust and of plethoric type and the local pain and chest oppression severe, the removal of a half pint of blood by phlebotomy may yield good results. It has the sanction of many authorities but the senior writer must confess he has never resorted to it, relying on other means to gain the same end. On the other hand, dry cupping is his practice (wet cups produce too many wounds). Cupping should not be limited to the supposed site of the inflammation but the cups should be applied all over the lungs, front and back, to the number of twenty or thirty. It should be done early and repeated every six or eight hours as long as pain persists, the dyspnœa or oppression continue, or the respiration rate rises. After cupping, the pain may further be relieved by thorough *strapping of the chest.* The fixation induced is of immense relief. External applications of sinapisms, liniments and ointments are of value for the friction required and the psychic effect induced. Dry cold, in the form of the ice-bag or the coil is in vogue at present and appears to relieve pain or limit congestion. The fact that it does induce comfort and is often grateful to the patient is a strong argument in its favor. Many do not like cold or are depressed by it. Dry heat, by hot water bags or flannels, gives comfort to many and for the aged and debilitated may be useful, although never a cure.

Hydrotherapy.—Greater confidence can be placed in hydrotherapeutic measures than in other forms of local treatment. These have the advantage of inducing peripheral stimulation and therefore also combating the toxæmia, for which general hydrotherapeutic measures also avail. We have the cold or warm bath and douches, the cold compresses, and the mustard foot bath, at our command. The *effect of baths* is to calm the nervous system, deepen respiration, aid expectoration, reduce fever, and stimulate the heart and vascular system, especially if not repeated oftener than every four hours.

Baruch points out that *in children* under eight years, the tub bath, 90° F., with friction, is of value, used for six to ten minutes when the temperature is above 102°, especially if there be nervous symptoms. It is well never to use water below 80° F. for children. If there are symptoms of heart failure—dyspnœa, cyanosis or other alarming manifestations—the child should be put in the tub with water at 100° F. up to the navel, and two to four basins of water (at 75° F. to 65° F.) poured over the shoulders. Then he should be dried with considerable friction. Jacobi advises "cold baths, or packs when the temperature is high, but most patients do quite well with sponging or friction with wet towels. The latter plan is both refrigerant and stimulant."

For adults the baths are too disturbing, although the temperature yields more readily than in typhoid fever. In severe cases with threatened collapse, however, a bath of 100° F. to the waist, and water 75° to 65° F. poured over the shoulders, is of value. It may be employed also when stupor is marked.

Cold compresses are efficacious methods of hydrotherapy and are applied as follows: Cut three thicknesses of old linen, of sufficient size to fit the entire chest from the clavicles down to the umbilicus, with slits in the region of the axillæ, made by exact measure, sufficiently deep to allow the upper edge of the compress to reach above the clavicles and admit of the junction of the flaps thus formed over the shoulders. Two such jackets and two pieces of closely woven thin flannel of the same shape but an inch wider should be provided and fitted. One of the linen compresses is rolled up, soaked in a basin of water at 60° F., and wrung out so that it remains quite damp, without dripping. The flannel is now spread out upon an even surface and the wet compress put upon it, so that there remains an edge of flannel about an inch wide all around. Both are rolled together half way. While the patient is turned upon his left side, without any effort on his part, the compress is so placed upon the bed that the rolled part lies in close proximity to the left side of the patient, the lower edge of the slit being under the axilla. The patient is then quietly turned upon his back, thus releasing the rolled-up portion, which is now unrolled, and the two edges thereof brought forward over the anterior surface of the chest until they meet. Next the flannel is laid over the compress, and attached in the median line with safety pins. The arms which have been elevated during this procedure are now laid at the patient's side.

The foregoing procedure is to be repeated every half hour unless the patient's temperature is below 102° F., and every hour unless it is below 99.5° F., when it should be discontinued. It should not be continued unless the patient feels warm before the application. Thinner compresses may be used for delicate individuals and changed as soon as they become heated. Oiled silk should never be used in the place of the flannel, as its use produces a poultice-like effect, entirely different from that which is desired. This treatment is especially efficacious in toning up the vasomotor system. It also furthers the elimination of toxin (Roque and Weil have shown that the toxicity of the urine is increased by it). Baruch has reduced his mortality in 156 cases about one-half, *i. e.*, to 12 per cent. in hospital practice.

Rationale of Method.—It has been shown experimentally that the pulmonary vessels are supplied by vasomotor nerves through the roots of the second to the seventh dorsal nerves. The "epigastric reflex" which resides in the skin of the epigastrium and sides of the chest, is connected with the fourth, fifth, sixth and seventh dorsal ganglia. Hence a positive effect upon the vasomotor supply of the lung may be evoked by covering the entire chest with sufficiently cold water to a line level with the umbilicus.

Baruch says, "When the cold compress is applied there is a rapid contraction of the cutaneous vessels which raises the tension at once, but eventuates in a tonic dilatation of these vessels, which is evidenced by the ruddy hue of the skin. This dilatation differs very decidedly from that relaxed condition of the cutaneous vessels which is produced by warm poultices. The latter relaxed condition produces a paretic condition of the vessels, or a stasis, while the cold applications stimulate the vasodilators, giving rise to an active dilatation, with maintenance of the tone of the vessels, an active hyperæmia, by reason of which the blood is propelled more vigorously through them. The heart is thus relieved; not by a *vis a tergo*, as is the case after digitalis, but by a diminished *vis a fronte*, formed by broadening of the blood stream, whose enhanced tonicity aids at the same

time in propelling the blood forward. Arterial tension is increased, as is evidenced by the better filling of the radial arteries. The right heart is indirectly aided by this enhancement of the general tone of the vascular apparatus, and may thus expend more force upon the pulmonary circulation, whose vessels contract more firmly by reason of the dilatation of the superficial vessels."

The senior writer has used these cold compresses in hospital and general practice for many years and can speak with positive confidence of their value. Sometimes the coil is substituted. In the wards of the Philadelphia hospital where many debilitated alcoholic and senile patients are brought, the treatment has been most satisfactory. Such individuals are also much benefited by stimulation by means of hot foot baths, or hot water bottles to the feet. The *mustard foot bath* should be given as follows: The patient, with the night-gown drawn up, lies upon his back, between blankets, the knees being flexed. A tub of water, as hot as the patient can bear, with its long axis parallel to that of the body, is placed under the feet. The vessel should be about half full of water and have added to it powdered mustard in the proportions of one tablespoonful to the gallon. A blanket should be placed under the tub and be folded over its lower end so as to cover the knees. Finally, several blankets or one blanket and a rubber sheet should cover in the patient, tub and all. As the water cools, additional hot water should be carefully added. The time required is generally about half an hour, varying according to the amount of sweating produced.

Cardiac Depressants and Hypnotics.—Measures to lower the blood pressure in the early stages are of doubtful usefulness and we must look upon such remedies as aconite and veratrum viride with many misgivings. It must be remembered that the use of the latter, particularly in a guarded manner, has the sanction of high authority, but such a view cannot be supported, as the same result may be obtained by safer measures. The severe rigor at the onset and the marked pain in the side contribute to shock the patient more or less. One plan, therefore, if the subject is not over fifty, is to give a full dose of morphia, preferably hypodermically. Repeated small doses are not as safe or as beneficial. Patients over fifty should be examined for renal disease before morphia is given, and to those with nephritis it should be given sparingly if at all. The morphia counteracts the shock, induces sleep and so indirectly relaxes the arteriovascular system as to lower blood pressure.

Laxatives, Diaphoretics and Diuretics.—In addition we have diuretics, diaphoretics, and laxatives. They each have a place in therapeutics of pneumonia. *Laxatives* may be employed in the first period. The infection is often attended by a slight gastritis with heavily furred tongue, anorexia and constipation. Small doses of calomel (gr. $\frac{1}{8}$, gm. 0.008) or mercury with chalk may be given hourly until a grain is taken. It is often advised to give calomel in one large dose (5 to 10 gr., 0.3 to 0.6 gm.) dry on the tongue. With or without calomel, Rochelle salts or saline cathartic waters may be given and repeated during the course of the disease, according to the indications. There are some who prefer to give robust subjects the compound cathartic pill or elaterium (gr. $\frac{1}{4}$ to $\frac{1}{3}$, gm. 0.016).

Of *diaphoretics*, the salts of potassium are the most satisfactory. Citrate of potassium (gr. 15, gm. 1) in hot water will lower blood pressure and so relax the vascular system as to induce sweating. Hot lemonade and other hot

drinks, hot water bags and mustard foot baths may start free perspiration. The hot pack or hot sweat may be employed with great caution. Jaborandi should not be given. One drug or combination of much advantage for its diaphoretic action and sedative effect, if pain is present, is Dover's powder. It should be given in small doses if there is pain and restlessness. One to three grains every three hours is sufficient. As soon as the pain is relieved it should be discontinued. The liquor ammonia acetatis may be given every second hour either with or without an opiate.

Diuretics.—These are in agreement with the other measures, as they lower blood pressure. Water is the best diuretic. From 4 to 8 ounces should be given hourly. The salts of potassium are useful diuretics. Unless there are complications it would not be wise to give digitalis or squill. These measures continued for two, three or more days, or as long as the fever lasts, unless replaced by drugs required for other indications, relieve the hot skin, the bounding pulse and the headache. If the urine is scanty, saline infusions may be used.

The Toxæmia.—This manifests itself first by an increased stimulation of the nervous system—wakefulness, excitability, delirium, etc. Later, the results of overstimulation become evident in enfeeblement, depression, hebetude, stupor or coma. The management of toxæmia consists in enforcing resistance, increasing elimination and counteracting the effects of the toxins. No antitoxin thus far obtained can be relied upon for therapeutic relief. Resistance to the toxins can be secured by aërotherapy, hydrotherapy, careful feeding and, when required, moderate stimulation.

Elimination is secured in the class of cases not overwhelmed at the onset, by the measures suggested to produce diuresis and diaphoresis. When indications of toxæmia, greater than the system of the patient can sustain, appear or failure of secretion of the urine is imminent, more energetic measures must be resorted to. Of these, hydrotherapy as described above, stands first. Not only is water to be used externally, but also internally. Large draughts of water—from 4 to 8 ounces—are to be given hourly or every second hour. It may be alkaline. Just as it is of value in typhoid fever, so it is of service in pneumonia. In severe forms, with renal insufficiency, enemas of normal salt solution (warm) may be given either high in the colon or by the constant method of Murphy. Likewise we may give saline infusions which in certain cases with marked toxæmia are of undoubted utility, but the mistake is often made of using them too late. The credit of instituting their use in pneumonia, as well as demonstrating the beneficial results, belongs to F. P. Henry. One often sees a very satisfactory result providing the procedure is not too long delayed, but we cannot subscribe to its efficacy with the same enthusiasm its earliest advocates claimed for it.

Elimination may be further induced by stimulants, as those employed to directly counteract the toxins, or by remedies as caffeine, cocaine or diuretin. It is usually not necessary to continue their use more than a few days. Coffee and tea should be used for this purpose, if they do not make the patient nervous. In cases of endocarditis with failing compensation, digitalis is the remedy to be used.

The effects of the toxins, if not lessened by elimination, must be counteracted by stimulants, given with full knowledge. The therapeutist has powerful weapons at hand. Alcohol, ammonia, strychnia, cardiac stimulants, camphor, musk and, for many, turpentine, compose the armamen-

tarium. They should not be used until needed, and then used without stint. Alcohol is best given as whisky or brandy. Four to 8 or even 12 ounces in twenty-four hours may be given. The minimum dose is to be preferred and can be deemed sufficient if sleep replaces delirium or wakefulness, if the tongue becomes moist, the pulse slower, the secretions more free, and the expression more natural; in short, if adynamia disappears and strength replaces exhaustion. Champagne may often lift the patient out of extreme exhaustion.

The advisability of administering alcohol in pneumonia has been much debated. On clinical grounds we are justified in giving this drug to those who are habitual users of it. Experimentally Colla found that its use tended to diminish the amount of glycogen in the liver, a substance which increased the resistance of rabbits to pneumococcus infection, but his findings were not corroborated by Luschi.[1]

Fock of Hamburg sent out blanks to a large number of physicians in Germany, Austria, Switzerland, Denmark, Sweden and England asking whether or not alcohol was given in every case of pneumonia, under what circumstances it was employed, in what form it was administered, whether it was given to drunkards, and what effects were expected and realized. The general conclusions which Fock draws from a large number of replies are that it makes little difference whether alcohol is used or not so far as the ultimate results are concerned. A number of the physicians were however under the impression that the use of this drug made convalescence more protracted.

Ammonia may be used as a stimulant, either constantly, at repeated intervals, or intermittently. We do not see the old ammonium carbonate bottle as frequently as formerly. Its place is limited to stimulation or when bronchitis complicates the pneumonia. The aromatic spirits of ammonia may be given regularly or when symptoms demand a rapid diffusible stimulant. It may be used to combat flatulence or acidity. It may be of much service if there is palpitation or dyspnœa in paroxysms. Camphor in oil is given hypodermically when there is adynamia with cerebral depression and cardiac exhaustion. Strychnia, hypodermically, should be given, especially if the pulse is rapid, feeble and dicrotic and the respirations hurried. It is not to be used in a routine manner.

The Crisis.—Caution and watchfulness must be enjoined at the expected time of, and in the event of, the crisis. The greatest care must be taken not to allow undue exertion, as sitting up in bed or straining at stool. Food must be administered in the recumbent posture and stimulants employed freely, usually in the diffusible form. Hot bottles or external heat in other forms should be applied and hot drinks given. Strychnia, and adrenalin or, if there be excessive sweating, atropine may be relied on to counteract the undue shock.

The Skin.—The usual care must be extended to the skin and especially in the pneumonia secondary to diabetes and chronic nephritis. The herpes requires anodyne dusting powders, as camphor, morphia and zinc oxide, sedative lotions, as camphor water or boracic acid in alcohol, or ointments, such as oxide of zinc and boric acid with or without morphia or cocaine.

The Nervous System.—The ice-cap or coil to the head is of much service. The extreme delirium of apex pneumonia usually does not require special

[1] *Jahresber. u. d. Fortschr. d. Thier.*, 1906, p. 349.

treatment. It must be distinguished from the delirium of meningitis, either from infection through the blood or from the ear and mastoid. The ear must be kept cleansed and any commencing infection thwarted by the application of leeches, ice, and by perforation of the ear drum or trephining of the mastoid as indicated. The delirium of alcoholism demands more active stimulation, which should be begun early. Postcritical delirium requires food and stimulants and may be aided by hyoscyamus, hyoscine hydrobromate or scopalamine. Large doses of bromides with trional may bring the desired sleep. Opium and morphia are usually not of service. The wet drip sheet may be required and is often effectual.

The Cardiovascular System.—Endocarditis in the course of pneumonia requires digitalis almost always, and especially if failing compensation is imminent. In the latter period of the disease dilatation of the right ventricle may ensue from mechanical causes, as well as because of the toxæmia. Local bleeding by leeches and perhaps generally by venesection may relieve the embarrassed heart. The cyanosis is removed, the empty thread-like pulse is improved and the respirations reduced in frequency. This condition may arise after the crisis. The symptoms of dilatation or of myocardial degeneration must not be confounded with somewhat similar symptoms due to pericarditis with effusion. If it is present, and the symptoms are alarming, aspiration or opening of the pericardium is imperative. It may be necessary to resect a rib. Pericarditis without effusion does not require any departure from the routine management, although the local application of cold may be tried. The myocardial weakness from toxæmia, which too often leads to cardiac paralysis, must be managed by the best of nursing, light feeding, and stimulation, through the free use of strychnia, camphor, ammonia, and adrenalin.

When the apex beat is feeble, the first sound weak, and accentuation, which has been present at the base especially at the pulmonary area, begins to fail, it should be considered a signal for stimulation. The condition of each patient must decide whether such stimulation should be directed chiefly toward the heart itself or to the vasomotors and the nervous system. It not rarely happens that heart weakness results from mechanical pressure from a pleural effusion or from distended intestines. In the first case, aspiration of the effusion, in the second, strychnia, eserine, turpentine stupes or enemata are indicated, with regulation of the diet. Cyanosis may be relieved by inhalations of oxygen, but it is very doubtful whether much is accomplished by this means.

The nitrites are sometimes employed with a view of lessening the burden of the heart, and certainly one does see patients in whom they improve the character of the pulse. This is chiefly early in the disease but later, when heart weakness is pronounced, this treatment is generally unwarranted because, owing to paresis of the vasomotor system, the blood pressure is already too low. Aromatic spirits of ammonia is often useful as a heart stimulant but the effect of this drug is temporary and the dose has to be repeated at frequent intervals. In treating the cardiac condition we should be careful to avoid overstimulation and from time to time change or alternate the various heart stimulants, as most of these are apt to lose their effect. Atropine is sometimes a useful drug, especially when œdema of the lung is threatened. Jacobi has very aptly said that the time to treat heart failure in pneumonia is before it has occurred, and while undoubtedly there is much

wholesome truth in the statement, it must not be misconstrued to mean that we should be too lavish with our heart stimulants. Only too often is it the case, that when the dire hours of the crisis arrive the heart fails to respond to treatment calling for renewed and redoubled effort. An ice-bag placed over the precordium is often of considerable benefit in slowing, strengthening and steadying heart action.

The Lungs.—If bronchitis is present expectorants must be used. Ammonium chloride may be given at first along with the diuretics and diaphoretics of the first period. Later, as expectoration is free, and the abundant rales indicate the second stage, stimulating expectorants may be given, as eucalyptus, turpentine and terebene. Of course, such remedies are not to be given if they interfere with the main indications for treatment. Large pleural effusions are to be aspirated and empyemas treated surgically as soon after the crisis, if it occurs, as possible.

The Gastro-intestinal Tract.—The question of *diet* is of the greatest importance. Nutrition should be kept up to the highest point. Formerly, as the result of misapplied treatment, it was not unusual for death to occur during convalescence, as the French put it "mort guéri." The food should be selected for its nutritional value, the ease of assimilation being equally considered. The ideal food, therefore, is milk in some form. This may be given plain, peptonized, diluted with lime-water or with some cereal added, or in the form of koumiss or junket. Gelatinous foods, broths or beef juice, may be alternated with the milk, but it should not be forgotten that, with the exception of the last of these, the nutritious value is much less than that of milk. As a general rule, sugars and starches are apt to produce fermentation, being therefore better omitted. Raw eggs, custards, scraped beef and ice-cream are allowable. Eggs may make up a large portion of the diet. In cases in which alcohol is indicated, this drug may be given incorporated with the food. Strong black coffee may be administered when heart failure or stupor calls for stimulation. All food should be given at regular intervals, varying from two to four hours according to the amount taken. Sleeping patients should not be aroused for nourishment, but stupor must not be confounded with restful sleep. Large amounts of water must be given and with this purpose in view the patient should have water offered to him at frequent intervals. Patients will often drink when a draught is thus presented, although they might not think of asking for it. The juice of oranges, grapes, lemons and shaddock are often relished and well borne. A very palatable diuretic beverage may be prepared by adding a teaspoonful of cream of tartar to a pint of boiling water, squeezing in the juice of half a lemon and serving when cold. The sucking of cracked ice is a procedure which is much relished and beneficial. Effervescent beverages are better omitted, especially if there is a tendency to flatulent distention. The various forms of predigested foods may be given, but it should be borne in mind that nearly all of them contain alcohol and relatively little nutriment. The same general rules apply in the case of *children*. If, as is sometimes the case, an infant is too ill to nurse, the mother's milk should be withdrawn by means of a breast pump and fed to the child a few drops at a time with a teaspoon. With older children fed upon cow's milk or artificial food, it is generally advisable to dilute the food.

In connection with the diet we have to consider the administration of *sodium chloride*. For some reason, not yet definitely known, during an

attack of pneumonia the chlorides are generally greatly diminished, often entirely absent from the urine for a number of days. It would seem rational, therefore, to suppose that these salts are required for some purpose by the economy. Some authorities have taken this fact as an indication for the exhibition of chlorides,—without any beneficial results, it must be admitted, but also without any deleterious ones. The salt may be given by being liberally added to the food or the beverages, by saline enema, or in capsule. Patients to whom sodium chloride is administered in this manner rarely show an entire absence of this salt from the urine.

The mild gastritis of the first period is to be treated by fractional doses of calomel and mild salines. The incessant vomiting of apex pneumonia may be relieved by ice compresses or mustard plasters. The diet should be much restricted and gastric sedatives employed. Colitis is a serious complication. Correction of diet is the first indication, careful high irrigation of the large bowel the second. Salt solution or boric acid solution may be used. Tympanites may ensue because of fermentation or of toxic paresis. For the former, restriction of the diet is necessary. The latter is an indication to increase stimulation and especially strychnine. The salicylate or nitrate of eserine physostigmine (gr. $\frac{1}{100}$ to $\frac{1}{40}$, gm. 0.00075) is often of value, given every four hours hypodermically. Jaundice is not likely to require special treatment.

The Genito-urinary Tract.—Nephritis in the course of pneumonia does not require special medication, as the diuretic and diaphoretic remedies and the measures to combat toxæmia suffice to meet the indications. Pneumonia occurring in a subject of chronic nephritis requires more alertness and more prompt measures to combat the toxæmia. It is a definite contra-indication for the use of opiates. Hot packs may be required.

As has already been stated the pneumococcus can be demonstrated in the blood in the great majority of cases, and it probably exists there in all of them. In pneumococcus septicæmia we have a general systemic intoxication, accompanied frequently by metastatic involvement of various tissues and organs. The symptoms of course depend largely upon the exact location of the inflammatory process. The treatment must vary accordingly; and beyond stating that this should be of a sustaining character no definite rules can be laid down.

Convalescence.—The management of convalescence depends on the complications and mixed infections that have arisen. Pneumonia uncomplicated is recovered from with rapidity and completeness. If the toxæmia has been great, the patient should be enjoined from work, especially mental, for a long time. No half-way measures should be advised. If cardiac complications occurred, the usual exercises and baths for this condition would be of service and timely. Pulmonary complications may require a change to a milder climate or to the sea.

Delayed Resolution.—The treatment of this condition must be directed toward improving the patient's general health and nutrition. A constant and liberal supply of fresh air must be supplied; pulmonary gymnastics may prove beneficial. Among the most generally applied measures are the external application of blisters, iodine, and the actual cautery, accompanied by the internal administration of the iodides. Some very convincing results have lately been reported by Edsall and Pemberton[1] who have applied

[1] *American Journal of the Medical Sciences*, February, 1907, p. 286.

x-rays to a number of these cases. There can no longer be any doubt that these rays exert a powerful influence upon metabolism, which they appear to stimulate, perhaps through their action upon various ferments. The cases reported by the above-mentioned investigators showed clinically a rapid clearing up of the consolidated areas, a condition which was accompanied by a very marked increase in the metabolic output through the urine. The general features in other words were practically identical with those noted in a normally resolving case of pneumonia.

Bearing these facts in mind we should be very chary about adopting the suggestion which has been made by some writers of employing the *x*-rays therapeutically while the disease is in the active stages. As we have already stated the chief danger to the patient at such times lies in the toxæmia of the disease, and by stimulating metabolic processes we should be running a grave risk of swamping the economy with a larger quantity of poisons than can be eliminated.

CHAPTER XXIV.

TOXÆMIA, SEPTICÆMIA AND PYÆMIA.

By RICHARD M. PEARCE, M.D.

Introduction—A consideration of toxæmia,[1] septicæmia and pyæmia is necessarily a discussion of infection and its sequelæ.

An *infection* is the condition produced by the entrance and growth within the body of pathogenic microörganisms. An infection may be local or general.

Toxæmia.—In a local infection the organisms multiply at the point of invasion, and cause, through the toxic substances which they elaborate, local tissue changes. At the same time these toxic substances pass into the general circulation and produce certain constitutional symptoms. This secondary condition is best described by the term *toxæmia*. Such is the usual course of events in the majority of acute infectious diseases, as diphtheria and the pyogenic infections. In some diseases, as tetanus, no demonstrable tissue changes occur at the site of inoculation, all symptoms being due to the intoxication resulting from the absorption of the bacterial products.

Although it is possible, as in the toxæmia of pregnancy, that substances elaborated in the destruction of tissue may cause an intoxication independent of bacterial action, we have little positive evidence that this is a common occurrence. It would seem advisable therefore to drop the old term *sapræmia* in favor of toxæmia. The term sapræmia, first applied to the group of symptoms supposed to be caused by the absorption of the products of decomposition, and used almost exclusively in a surgical sense, does not accurately characterize the general group of intoxications due to bacterial products and of interest now to the physician as well as to the surgeon.

Bacterial intoxication, however, may occur in the absence of infection, for example, in the various forms of food poisoning. Under these circumstances the symptoms due to a poison introduced in large amount into the gastro-intestinal canal depend only upon the rapidity and amount of absorption; infection does not occur, for the organism which produced the toxic substance, even if present, does not invade the tissues. It is essential therefore in considering bacterial intoxications to distinguish between those following infection and preceded by a period of incubation and those due to the absorption of preformed toxins without infection. The latter are limited practically to the group of food-poisonings and do not come within the scope of this discussion.

Septicæmia.—The older conception of septicæmia as a surgical affection due to the invasion of the blood by the organisms of suppuration has delayed

[1]The term toxæmia is used here to include only those forms of intoxication due to the products of bacteria; other forms due to altered metabolism, as for example the toxæmia of pregnancy and the various cachexias, do not come within the scope of this section.

the acceptance of the term in its broader meaning. The general invasion of the blood and tissues by any of the pathogenic bacteria constitutes a septicæmia and it matters not whether the general infection follows local suppuration, or some other disease as gonorrhœa or pneumonia, or even develops without evident portal of entry. The application of the term *bacteriæmia* to this condition is an attempt to avoid the older terminology. The constitutional symptoms of a septicæmia are naturally those of toxæmia and due to the same factor, *i.e.*, the poison elaborated by the infecting organism. There is however this difference: in toxæmia the poison is formed in the wound and absorbed therefrom, while in septicæmia it may also be formed in all parts of the body. In the former the symptoms usually disappear with the removal of the local infection while in the latter such removal, once the process is well established, has little or no effect.

Pyæmia.—When, in the course of a general invasion of the blood and tissues by a pathogenic microörganism, multiple secondary foci of suppuration appear, the condition becomes a pyæmia. These secondary foci include abscess, diffuse suppuration, endocarditis, synovitis or any other inflammatory condition of either the solid structures or the body cavities. The term pyæmia therefore includes more than the mere development of secondary abscesses. For example, a gonococcus septicæmia accompanied by an ulcerative endocarditis and suppuration in the joints, due to the same organism as a result of its dissemination in the blood is, strictly speaking, a pyæmia although abscesses in the ordinary sense may not be present.

While in the majority of pyæmias the secondary lesions are due either to the streptococcus or the *Staphylococcus pyogenes aureus*, other organisms as the pneumococcus, the gonococcus and the colon and typhoid bacilli may produce suppuration. The distribution of the infecting organism is frequently accomplished by fragments of thrombi, which, becoming separated from the local lesions, pass as emboli to various parts of the body and, if conditions are favorable, cause suppuration wherever they lodge. Pyæmia obviously includes both septicæmia and toxæmia.

Boldt suggests for septicæmia the term acute bacteriæmia and for pyæmia, chronic bacteriæmia—but both clinically and pathologically this nomenclature appears to be of doubtful value.

Historical.—Previous to the development of bacteriology the theories concerning wound suppuration and its complications were naturally based on anatomical observations. Pyæmia therefore received early attention, while the explanation of septicæmia and toxæmia was delayed until the advent of bacteriology.[1]

The first attempt to explain the secondary abscesses was made by Boerhaeve who, in 1720, affirmed that these were due to a contamination of the blood by the pus of the wound. In 1774 John Hunter demonstrated the association of suppurative phlebitis and pyæmia. He believed that pus was secreted by the vein wall, and therefore considered the phlebitis to be an intermediate stage necessary to the development of secondary abscesses. This idea was supported by Cruveilhier in 1826. Virchow in 1846 opposed the theory that pus enters the circulation from the veins, and pointed out

[1] For good histological reviews see W. Watson Cheyne, "Suppuration and Septic Diseases," Edinburgh and London, 1889; ibid, "Septicæmia and Pyæmia," Allbutt's *System of Medicine*, 1896, i, 586; also v. Kahlden, "Sepsis," Eulenberg's *Real Encyclopädie der gesammten Heilkunde*, 1899, xxii, 329.

that the material in the veins is not pus but softened and altered thrombi and that the softened thrombi are separated from the circulating blood by more recent clots. He also expressed the opinion that the increase of so-called pus cells in the blood was evidence of a leukocytosis, and not of the absorption of pus from the local lesion. In the meantime several investigators (Gunther, Castelnau and Ducrest) had produced metastatic abscesses by injecting pus into the veins of animals. The recognition of a general toxic condition independent of the local suppuration of pyæmia was largely due to the work of D'Arcet (1842), who asserted that in septic infections two associated but distinct processes exist, a general poisoning due to the absorption of putrid products and plugging of the vessels by emboli. The first explained the fever and constitutional symptoms, the second the metastatic abscesses. Virchow demonstrated later that the general septic condition could occur without metastatic abscesses; thus he distinguished between septicæmia and pyæmia as we now use the terms. The experiments in support of this view were made with putrid pus. It was found that well-filtered pus caused only the constitutional symptoms; while unfiltered pus, containing small masses of cells, led to the formation of embolic abscesses.

Meanwhile, early in the nineteenth century, several investigators had studied experimentally the effect of injecting infusions of putrid meat and other substances. The first attempt to isolate the toxic chemical bodies from such fluids was made by Panum in 1856. He found that the toxic property of putrescent fluids was unaltered by heat, and was able to extract with alcohol a substance of considerable toxicity for dogs and causing symptoms of putrid intoxication. Bergmann and Schmiedeberg, in 1868, isolated from putrid yeast and from decomposed blood a crystalline substance which they called "sepsin" and believed to be Panum's putrid poison. Levy, later, brought forth evidence which indicated that sepsin is a product of the *B. proteus*. These and other investigations which followed, although they led eventually to the discovery of ptomains and to the elucidation of the various forms of food poisoning, aided in the solution of the problems of septicæmia only by the impetus they gave to the study of bacterial products.

A little later the rapid advance of bacteriology allowed the application of methods which soon demonstrated the true nature of wound infection and its sequelæ—toxæmia, septicæmia and pyæmia—and eventually to Lister's statement of the principles of antisepsis. Of these investigations the more important were those of Rindfleisch, v. Recklinghausen, Waldeyer, Klebs, Pasteur, Burton-Sanderson, and Koch.

To Koch, especially, is due the credit of experimentally distinguishing between septic intoxication and true septicæmia and the relation of pyæmia to the latter. He was able to demonstrate the rapid toxic action of large doses of putrid fluids with fatal result within a few hours; and with small doses, one to two minims in mice, a gradual onset of symptoms, which developed in about twenty-four hours and usually resulted fatally. The blood of the latter animals contained bacteria which he was able to cultivate. With minute amounts of these cultures he reproduced the disease, thus demonstrating that septicæmia was a true general infection differing from putrid intoxication in which he found no organisms in the blood. He also demonstrated, in a micrococcus septicæmia, a plugging of the vessels by

emboli composed of colonies of cocci and adherent red blood corpuscles, a condition somewhat analogous to the closure of vessels by embolic portions of infected thrombi.

Etiology.—Toxæmia.—Under this term may be included all intoxications due to the absorption of bacterial poisons. For convenience of description two sub-divisions may be made: (1) the toxæmias associated with affections demanding surgical intervention, the so-called "sapræmia;" and (2) those of the acute infectious diseases as diphtheria, typhoid fever and pneumonia. The toxæmias of the first group are more or less uniform in character, for they follow either the invasion of living tissues by pyogenic organisms or the activity of putrefactive bacteria in necrotic tissues. The toxæmias of the second group, due as they are to widely different microorganisms, vary according to the character of the toxin produced. It therefore follows as a general rule that the toxæmia of any given infection is responsible in a great degree for the more important constitutional symptoms. For this reason it is worth while to consider the nature and mode of action of the products of bacterial activity.

The Bacterial Poisons.—That the characteristic effects of a pathogenic microörganism are due to the chemical substances which it elaborates is now generally accepted. This may be manifest not only in the character of the local lesion but also in the degree and nature of the constitutional disturbance. Thus in typhoid fever, cholera, diphtheria and pneumonia, though each has a distinctive local lesion, widespread systematic disturbances occur; on the other hand in gonorrhœa, except in peculiarly virulent infections, the action of the poison is confined to the place of its formation. Some organisms in addition to the production of a general toxin also produce a special poison as shown by the peculiar involvement of the peripheral nerves in diphtheria and the motor neurones in tetanus.

A distinction may be made between pathogenic and toxicogenic bacteria. "A pathogenic bacterium is one which induces a specific disease recognized by more or less well marked and characteristic symptoms during life, by more or less definite lesions found after death, or by both. Pathogenic bacteria are always capable of growth in the animal body, in which they multiply and elaborate their specific toxins. All pathogenic germs are toxicogenic, but it does not follow that all toxicogenic bacteria are pathogenic. A toxicogenic microörganism is one which is capable of producing a poison or poisons. A toxicogenic germ may or may not be capable of growth in the animal body. It may multiply in milk or some other article of food before its introduction into the body, and may in this menstruum elaborate more or less powerful poisons."[1]

The substances resulting from bacterial activity may be conveniently grouped as ptomains and toxins. Vaughan and Novy define a ptomain as "an organic chemical compound, basic in character, and formed by the action of bacteria on nitrogenous matter." These substances are also called putrefactive alkaloids. Kobert had applied the term "ptomatin" which he considers to be etymologically preferable. The ptomains are to be regarded as "extracellular products of bacterial activity. They do not

[1] Vaughan and Novy, *Cellular Toxins or the Chemical Factors in the Causation of Disease*, 1902. To this work without further reference, I acknowledge my indebtedness for much that is contained in the following pages devoted to a description of the bacterial products.

originate within the bacterial cell and therefore are not to be looked upon as direct metabolic products of the cell protoplasm but rather as secondary cleavage products." They are formed almost exclusively outside the living body and therefore play but a small part in producing pathological conditions. When however they are ingested with food, they cause an acute, severe and frequently fatal intoxication. With meat poisoning or botulismus is associated especially *B. botulinus*. Van Ermengen has shown that the toxic substance of this organism is almost as powerful as that of the tetanus bacillus. Kaensche's researches show that at least three different bacilli may produce toxic substances in decomposing meat. Many of the ptomains resemble certain vegetable alkaloids in either their chemical or physiological reactions. Some may be obtained from a variety of decomposing substances, irrespective of the type of organisms present. Others appear to be associated with the growth of certain organisms, as cadaverin with the genus vibrio, tetanotoxin, spasmotoxin and tetanin (Brieger) with the *B. tetani*, the poison of cheese (tyrotoxicon) with members of the colon group (Vaughan) and pyocyanin with the *B. pyocyaneus*.

The toxins, unlike the ptomains, are the result of synthetical processes occurring within the bacterial cell. They are all, probably, proteid substances and may be divided into toxins, toxalbumins and bacterioproteins. Toxins and toxalbumins are soluble, the former of unknown chemical composition, the latter partaking of the chemical nature of albumins. The bacterioproteins are the proteid elements of the bacterial cell. Here, however, the term toxin will be used in a general way to indicate the toxic products of bacteria without regard to their chemistry or their power to stimulate the formation of an antitoxin. It is customary to distinguish between extra- and intracellular toxins. By the former we mean those soluble chemical substances which are found in the filtrate of the fluid in which the bacilli have grown and which represent the result of synthetical processes in the cell. To this group belong especially the toxins of the diphtheria and tetanus bacilli. Some organisms however yield a toxic substance only upon the disintegration of the bacterial cell. These are known as intracellular toxins or endotoxins and to this group belong the majority. A distinction is sometimes made between specific and non-specific toxins. The tetanus toxin, for example, which is peculiar to the organism which generates it and has an affinity for the motor neurones, is said to be specific; while a toxin which is similar in nature and action to the products of a number of other organisms is non-specific.

In the following paragraphs our knowledge of the more important bacterial poisons is summarized.

Staphylococcus Pyogenes Aureus.—Filtered products of this organism have little toxic effect, the poison being an intracellular one. Leber in 1884 induced suppuration by injecting boiled cultures of the *Staphylococcus pyogenes aureus* and later prepared from the same organism an alcoholic extract also pyogenetic. From various bacteria (including *S. pyogenes aureus* and *B. pyocyaneus*) Buchner obtained proteids which were pyogenetic, exerted a positive chemotoxis upon leukocytes, and caused, when injected into a vein, a general leukocytosis. The injection of a very small amount of this proteid beneath the skin of the forearm produced a typical erysipelatous inflammation about the site of inoculation with involvement of the lymphatics. Mannotti working with sterilized pus and dead cultures

of the *Staphylococcus pyogenes aureus* has produced, by repeated injections, a grave form of chronic intoxication and marasmus, analogous to that observed in man as the result of chronic suppuration. Van de Velde has observed that the staphylococcus produces a substance which rapidly destroys leukocytes and to which the name leukocidin is applied. An hæmolysin produced by this organism and known as staphylolysin has been thoroughly studied by Neisser and Wechsberg. The work of Ribbert with dead cultures of the staphylococcus and of Neisser and Wechsberg with staphylotoxin indicate the grave lesions which may be produced in the kidney by the products of this organism. Chronic renal changes have been described by Morse.

Micrococcus Gonorrhœæ.—The gonotoxin has been studied by Christmas, Nikolaysen and Wasserman. Cultures destroyed by heat are as virulent to the lower animals as are the living cultures. The poison is an intracellular toxin. Subcutaneous injections in animals cause local induration and necrosis; large doses lead to chronic marasmus and death. Intra-ocular injections produce hypopyon and occasionally complete loss of the eye. Wasserman injected 0.1 cc. beneath the skin of his arm. A local reaction with light chills, slight rise in temperature, headache and pains in the joints followed. Gonotoxin introduced into the healthy urethra of man produces suppuration.

B. Tetani.—The tetanus toxin is readily produced by growing the organism in bouillon and is the most powerful of the bacterial poisons. The recent work of Ehrlich and of Madsen has shown that the tetanus bacillus produces two distinct bodies, tetanospasmin which has an affinity for the nerve cells and tetanolysin which causes a solution of the red blood corpuscles. Each of these bodies has its own specific antitoxin.

Tetanus toxin produces its characteristic symptoms only when introduced into the circulation. While it is usually possible to demonstrate the presence of the toxin in the blood of the general circulation, it is found in largest amount in the central nervous system, for the cells of which, it has a special affinity as first shown by Bruschettini and Dönitz. The experiments of Wasserman and Takaki not only support this view but show that the toxin unites in vitro with the nerve cells to form a compound, which, when injected into susceptible animals, is without toxic effect. Dönitz has produced in animals by the injection of minute doses of tetanus toxin a fatal marasmus without tetanic symptoms.

B. Diphtheriæ.—The diphtheria toxin is the type of soluble extracellular toxin. It is readily obtained by filtering bouillon in which the diphtheria bacillus has been allowed to grow for several weeks. The toxin has also been extracted from fragments of diphtheritic membrane. It is very powerful in its lethal action, 0.0005 cc. killing a guinea-pig of 300 grams. The experimental lesions observed in animals consist of œdema at the point of inoculation, serous exudate in the plural and peritoneal cavities, fatty changes in the liver and kidneys and usually hyperæmia of the adrenals. In animals which do not succumb in a short time, paralysis, especially of the extremities, may develop. The diphtheria toxin has been more extensively studied than any other of the bacterial poisons, especially by Ehrlich and his pupils, who ascribe to it a complex constitution.

B. Tuberculosis.—The toxic principles of this organism are contained in tuberculin, a crude substance obtained from large quantities of the bacilli

grown on the surface of glycerine bouillon and after concentration filtered through a Pasteur-Chamberland filter. Injected into normal animals it produces little or no effect, but in either man or animals affected by tuberculosis it produces the febrile reaction and local tissue changes well known as the tuberculin reaction. The local reaction consists of hyperæmia and exudation from the vessels and a disintegration of the cells of the tuberculous focus. The products of this disintegration cause, it is supposed, the febrile reaction. Concerning the systemic action of the toxin formed in the course of the disease we have little knowledge.

B. Mallei.—From cultures of the bacillus of glanders may be obtained a substance, mallein, which has the same relation to this disease that tuberculin has to tuberculosis.

B. Typhosus.—The toxin of this bacillus belongs to the group of intracellular poisons. Pfeiffer and Rolle by disintegrating large quantities of the bacilli grown on agar were able to procure a substance fatal to guinea-pigs in dose of 4 mg. per 100 grams of body weight. With this substance animals could be immunized against typhoid fever. The ptomain previously isolated by Brieger, and named by him typhotoxin, has been shown not to be the essential toxic principle.

Streptococcus Pyogenes.—Simon in a review of the streptococcus toxins came to the conclusion that outside of the living body these bacteria produce no soluble toxin and only an exceedingly weak and uncertain intracellular toxin. The mild toxic substance which he produced by growing streptococci in bouillon containing pleural leukocytic exudate was not analogous to other known toxins. MacFadyan and Rowland, by grinding streptococci frozen by liquid air, extracted with salt solution a toxic substance, one-tenth cubic centimeter of which killed a guinea-pig in six hours. A hæmolytic substance (streptocolysin) has been studied by Besredka, Simon and Ruediger. The latter, who has recently reviewed the mechanism of streptococcus infection, offers evidence that the streptococcus produces a substance toxic for leukocytes, and on the other hand that phagocytosis is the most important process by which the body combats streptococcus infections.

B. Coli.—Vaughan and Cooley from large quantities of colon bacilli have extracted an intracellular toxin 0.0002 grams of which will kill a 200 gram guinea-pig.

Of the toxins of other bacteria, despite the enormous amount of work which has been done, we have little accurate knowledge. No organism, with the exception perhaps of the diphtheria and tetanus bacilli, has been so thoroughly investigated as the anthrax bacillus, yet Conradi, after exhausting all known methods, was unable to show that this organism forms either an extra- or intracellular poison. Recently, however, J. Walter Vaughan has shown that an intracellular poison may be isolated. Many organisms which produce clinically a well-marked toxæmia do not readily yield toxins by ordinary laboratory methods. The newer methods described by Conradi, Brieger and Mayer, and Neisser and Shiga of obtaining toxins by autolysis and MacFadyan's methods of mechanical disintegration offer promise of greater success in the near future.

Already Vaughan and his associates have thrown much light on the intracellular toxins of not only pathogenic organisms but also of some supposed to be non-pathogenic. By growing bacteria on solid media in large tanks they have been able to procure the cell substance in quantities sufficient to

enable them to study its constitution. The colon bacillus, the bacilli of diphtheria and anthrax, the *B. pyocyaneus*, the *Micrococcus prodigiosus* and several sarcinæ have been studied in this way. The cell substance of each was found to be more or less toxic to guinea-pigs and rabbits. As the result of an extensive study of the chemistry of the colon bacillus Vaughan reaches the following conclusions which, he believes, may apply to all bacteria:

1. The colon bacillus in its essential part is a chemical compound as truly as sodium sulphate or phenylhydrazin.

2. The colon molecule contains the following groups: nuclein, amido, diamido, monoamido, carbohydrate, toxic, hæmolytic, and hæmoglobin-splitting groups. There may be, and probably are, many other groups.

3. That these groups are chemically combined in the cell is indicated by the fact that they are not extracted by agents acting physically as solvents, but are separated only by those agents which split up molecules.

Considerable interest has been added to the study of the metabolic products of bacteria by the observations of Ehrlich and Madsen that some organisms produce an hæmolysin. There is considerable evidence however, of which the most important is that presented by Jordan and Williamson, that the hæmolysis produced by bacterial filtrates is to be explained by the presence of an alkali elaborated in the growth of the organism. Of all the bacterial hæmolysins which have been described the only one which produces an evident destruction of the blood in the living animal is the *B. megaterium*. Several investigators have also described hæmagglutinins of bacterial origin.

Septicæmia and Pyæmia.—As pyæmia depends on an antecedent septicæmia, the etiology of these two conditions may be considered in common. The septicæmias may be divided into those following a definite local infection and those developing in the absence of a recognizable portal of infection. In the first group we have the general invasion of the blood from such lesions as pneumonia, typhoid fever, diphtheria, gonorrhœa, anthrax, puerperal fever and various suppurations. The septicæmia under such circumstances may be due to the organism causing the primary lesion, as a pneumococcæmia in association with lobar pneumonia; or it may be due to a secondary invasion, as a streptococcæmia in diphtheria. The latter type is not infrequent in diphtheria, scarlet fever, smallpox, and tuberculosis. The organisms which have been found in septicæmias of unknown origin are, in the order of the frequency of their occurrence, the streptococcus, the staphylococcus, the pneumococcus, the typhoid bacillus, the colon bacillus and the *B. pyocyaneus*.

Of supreme importance in the study of septicæmia has been the determination of the organisms capable of producing a general infection. The early work concerning the relation of local suppuration to septicæmia and pyæmia contains many references to bacteriological examinations. In some instances this included only a determination of the organism in the local lesions, while in others an attempt was made to correlate the findings in the primary infection and in the secondary pyæmic foci. Although this is of importance, as is also the data obtained by the routine bacteriological examination of the blood and organs at autopsy, the greatest progress has been made as the result of the examination of the blood during life.

An exhaustive consideration of the bacteriology of the septicæmias, especially of those forms occurring in surgical and obstetrical practice,

would be too bulky for the present discussion.[1] The relation of the streptococcus, the *Staphylococcus aureus* and less frequently the pneumococcus and colon bacillus to these has been definitely established. Cabot (1904) has summarized a score of the more important investigations covering conditions usually termed "septic" by the surgeon or obstetrician and including endocarditis and suppurative arthritis. He finds a total of 316 examinations with positive results in 107, or 33 per cent.

The bacteriæmias occurring in medical practice however deserve special consideration. A clinical rather than a bacteriological classification offers the best basis for discussing these.

Pneumonia.—That a pneumococcæmia, analogous to the similar condition produced in animals experimentally, may occur quite constantly has been demonstrated in a very extensive series of investigations of the blood. Ewing in 1902 summarized twelve of the more important studies. These gave a total of 348 cases, in 160 of which the pneumococcus was isolated from the blood. Of these 160 cases, 64 ended fatally; while of the 188 in which the blood cultures were sterile, 37 died. Simon states that blood cultures give positive results in 50 per cent. of the fatal cases. Boulay considers the organisms isolated but a few hours before death to be the result of antemortem (agonal) invasion. Prochaska, who found the pneumococcus in all of 50 cases examined, believes the invasion to be a constant condition in pneumonia, as does Rosenow who obtained positive results in 77 of 83 cases in which the blood was taken at all stages of the disease. Pearce in a study of 118 cases of lobar pneumonia at autopsy found the pneumococcus in the hearts' blood, liver, spleen or kidney in a little less than one-half of the cases.

Pneumococcæmia without distinct localizations has been reported by Wright and Stokes, Pearce, Flexner, Hektoen and others. This is not an unusual form of terminal infection. In connection with bronchopneumonia, general infection with the pneumococcus, the streptococcus, the *Staphylococcus pyogenes aureus* or Friedländer's bacillus may occur.

Influenza.—Pfeiffer has found the *B. influenzæ* in the spleen, and Canon in the blood, of persons with influenza; while Jehle had found it in the blood in various of the acute infectious diseases of children (diphtheria, scarlet fever, measles, and varicella). Austin describes 3 cases of endocarditis in which a bacillus resembling that of influenza was found in films prepared from the vegetations; it was not obtained in cultures. That in these cases a true septicæmia existed is supported by the investigation of Slawyk and Pfuhl. On the other hand Pfeiffer and Kruse deny the identity of some of the organisms isolated by others, and Kühnau reports negative results in 12 cases.

Diphtheria.—The diphtheria bacillus for a time was supposed to cause a pure toxæmia without systemic bacterial invasion. Frosch, in 1893, first demonstrated the escape of the bacilli into the blood and tissues and his observations were quickly confirmed by Wright, Kanthack and Stephens, Nowak, Pearce and others. Councilman, Mallory and Pearce in a study of 220 fatal cases of diphtheria, found the diphtheria bacillus in the blood or internal organs in 36 of 59 cases of diphtheria complicated by scarlet fever or

[1]For the general literature of this subject see Kühnau, *Zeitschr. f. Hygiene u. Infektionsk.*, 1897, xxv, 492; Kahlden, *loc. cit.;* Rosenberger, *Proceedings of the Philadelphia Pathological Society*, 1903, vol. vi, 157.

measles, and in 83 of 161 cases of diphtheria only. In but a small proportion did it occur in pure cultures. The associated organisms were the streptococcus, the *Staphylococcus pyogenes aureus* and the pneumococcus. All investigators agree that the most frequent form of general infection in diphtheria is streptococcæmia. The possibility of the *B. diphtheriæ* producing pyæmia is suggested by Howard's case of endocarditis and a few other instances of secondary suppuration due to this organism. The pyæmia of diphtheria is however as a rule due to secondary infection by cocci. As far as known to the writer, Neisser alone has cultivated the *B. diphtheriæ* from the blood during life.

Scarlet Fever.—So constant is the presence of the streptococcus in scarlet fever that some investigators believe it to be the cause of the disease. While, however, definite evidence of an etiological relation is lacking, it is found to be the most frequent form of general infection and the cause of the great majority of secondary inflammatory complications. For example, in fatal cases Babes found it in the blood or internal organs in 17 cases, Pearce in 11 of 23 cases, Baginsky and Sommerfeld in all of 82 cases, Slawyk in 45 of 98 cases. The isolation of the streptococcus from the blood during life has been thoroughly studied by Hektoen, who gives also the most satisfactory opinion concerning the streptococcæmia of scarlet fever. Although most observers have had indifferent success in cultivating the organism from the blood, Hektoen obtained positive results in 15 of 100 cases. Our present attitude concerning the streptococcus and scarlet fever may best be expressed in Hektoen's conclusions:

"The conclusions that suggest themselves from this work so far as scarlatinal streptococcæmia is concerned are that streptococci occasionally may be found in the blood of cases of scarlet fever that run a short, mild and uncomplicated clinical course; that streptococci occur with relatively greater frequency in the more severe and protracted cases of scarlet fever in which there also may develop local complications and clinical signs of general infection, such as joint inflammations, but even in the grave cases of this kind spontaneous recovery may take place; and finally, that streptococcæmia may not be demonstrable in fatal cases of scarlet fever. The theory that scarlet fever is a streptococcus disease does not seem to receive any direct support from this work."

General invasion by the staphylococcus, the pneumococcus and the bacillus of influenza may also occur in scarlet fever. The occurrence of the latter in various acute diseases of children has been emphasized by Jehle, while the first and second have not infrequently been described. These forms of septicæmia, however, are not so peculiarly associated with the disease as is that due to the streptococcus.

Smallpox.—To this disease the streptococcus bears the same relation as it does to scarlet fever. It is the usual cause of the secondary inflammatory complication and very commonly of a general infection. Ewing found the streptococcus in the heart blood of all of 29 cases of smallpox; while Perkins and Pay cultivated it from the various organs in 38 of 40 fatal cases and from the blood in 11 of 20 cases during life or shortly after death.

Gonorrhœa.—While in the vast majority of cases gonorrhœa remains a disease of mucous membranes, we find occasionally a true gonococcæmia. These cases are usually pyæmic in a strict sense, as they exhibit secondary inflammatory lesions, as endocarditis, phlebitis, synovitis or arthritis.

The most complete study of this condition has been made by Thayer, who, working with Blumer (1895), first demonstrated the relation of the gonococcus to endocarditis and cultivated the organism from the blood during life; later with Lazear, he reported a second case. To these Lartigau in 1901 added another and four other cases are noted by Rosenberger (1903), while not a few cases have recently been reported by French and German investigators.

Acute Endocarditis.—While a primary simple endocarditis is still recognized, it is probable that this, like the malignant form, is the result of a bacteriæmia. The infection can be explained only by assuming that microörganisms reach the endocardium through the blood stream. Whether the infection results from an advanced septicæmia or from a few stray organisms, the lesion of the valve affords a nidus favorable to the continuance of the general infection or capable of causing its exacerbation. We may conclude therefore that the presence of an organism in an endocarditis is evidence of its power to produce a septicæmia. The forms usually found are the streptococcus, the staphylococcus, the pneumococcus, and the gonococcus; occasionally the *B. typhosus, B. coli, B. diphtheriæ, B. tuberculosis, B. influenzæ, B. pyocyaneus* and the meningococcus.

Typhoid Fever and Paratyphoid Injection.—Previous to the observations of Kühnau, in 1897, typhoid fever was supposed to be a true toxæmia but he, by diluting the blood with large quantities of bouillon and making many plates, was able to obtain the organism from 11 of 41 cases examined. The collected cases, now numbering over 500, indicate that in typhoid fever a bacillæmia exists in about four-fifths of the cases. Corroborative evidence of the frequency of this condition is shown by the fact that bacilli are found in the rose spots in about the same proportion.

Of special interest are those cases of typhoid septicæmia in which no intestinal lesions exist. Such cases present a typical clinical history, a positive Widal reaction, and the bacilli may be cultivated from the blood. The importance of this condition was first emphasized by Chiari and Kraus, and later in this country, by Flexner. In these cases special local lesions may occur in other organs than the intestine, as the lung or cerebral meninges. Whether such localizations are to be considered as secondary to the septicæmia and therefore pyæmic in character is not clear.

Through the application of more exact bacteriological methods and especially of comparative agglutinative tests we now recognize a group of bacteria resembling the *B. typhosus* and causing a clinical picture similar to that of typhoid but without the local lesions and known as "paratyphoid fever." In many instances these organisms have been isolated from the blood.

Post-typhoid septicæmia and pyæmia are usually due to a secondary invasion of pyogenic cocci, especially the streptococcus, the staphylococcus and the pneumococcus. The secondary suppuration may occasionally be due to the typhoid bacillus, but the damage is usually caused by cocci.

Tuberculosis.—While our knowledge of the dissemination of tuberculosis within the body affords evidence of the occasional escape of a few bacilli from the local lesions into the blood, it is only in the acute miliary form of the disease that we have a true septicæmia. Indeed in this disease with its local lesion, a bacteriæmia and a secondary eruption of tubercles, we have the same infection-mechanism as in ordinary pyæmia; the only

difference lies in the histology of the lesions, one being as a rule a proliferative, the other an exudative process. In acute miliary tuberculosis, tubercle bacilli may occasionally be found in laked and centrifuged blood or in the digested clot; the search, however, is most tedious and of doubtful utility. According to Liebmann the bacilli are found most frequently twenty-four hours after the injection of tuberculin. He claims to have found them under such circumstances in 56 of 141 cases. The later negative results of Guttman and of Kossel, however, suggest the possibility of contamination. The generally negative results obtained by inoculating animals with the blood of the tuberculous do not encourage these examinations.

Of great importance, from the clinical point of view, are the various forms of mixed infection which may occur in the late stages of the disease, especially in pulmonary tuberculosis with extensive ulceration. The toxæmia or bacteriæmia thus produced may cause exceedingly confusing symptoms. Sata, who has studied these mixed infections thoroughly, states that the organisms most frequently found are the *Streptococcus pyogenes*, *Staphylococcus pyogenes aureus*, *Diplococcus pneumoniæ*, and the pneumobacillus and allied capsulated organisms.

Acute Articular Rheumatism.—Frequently the clinical picture of this affection closely resembles that of a septicæmia, and the isolation of microorganisms offers some support of such a view. Streptococci, staphylococci and various bacilli, some of the colon type, and others anaërobic and bearing spores, have been found. The more recent and critical publications on the subject are those of Beattie, Lewis and Longcope, and Cole. The bacilli are found to have no constant relation to the disease and opinion varies as regards the cocci. Beattie and others hold that the "Micrococcus rheumaticus" is distinct from the ordinary streptococcus and is the specific cause of the disease; in animals it causes articular and cardiac lesions and chorea. In this he supports the opinion of Poynton and Paine, Wassermann and Myer, and others. Singer considers the presence of the streptococcus to indicate that the disease is a form of septicæmia with pyæmic manifestations. Cole finds that the lesions produced by the "Micrococcus rheumaticus" may be produced by streptococci from various sources.

Anthrax.—In man the local lesion, malignant pustule, if not excised early, is practically always followed by a fatal septicæmia. Under such circumstances the anthrax bacillus may occasionally be demonstrated in blood films or in cultures from the blood; a more satisfactory method, however, is the inoculation of an animal with the blood.

Bubonic Plague.—Bacillæmia occurs in this disease, according to Atkinson's figures, in about 80 per cent. of the cases. Ewing found the bacilli in 90 per cent. of the cases near death, and earlier in the disease in 60 per cent.

Bacillus Pyocyaneus Infections.—Under the term pyocyanic disease, or cyano-pyæmia, are grouped a variety of infections, usually local, occasionally general, due to the *B. pyocyaneus*. As a rule the general infection has been demonstrated by bacteriological examinations after death, though at least one observer, Blum, has obtained the organism from the blood during life and has demonstrated its relation to endocarditis.

Hemorrhagic Septicæmia Due to Capsulated Bacilli.—Howard has described a type of septicæmia characterized by hemorrhage into the skin, serous membranes, and various organs, in which capsulated bacilli (*Bacillus*

mucosus capsulatus group) are found either alone or as the predominating organism of a mixed infection. A bacillus (Friedländer's) of this group has been isolated from the blood during life, usually in cases of bacillæmia associated with pneumonia, by Beco, Phillipi, and Boston. The occurrence of true pyæmia due to Friedländer's bacillus has been emphasized by Etienne.

Other organisms which have been obtained from the blood during life are the *B. mallei, B. leprœ, Diplococcus intracellularis meningitidis, B. aërogenes capsulatus, Micrococcus zymogenes* and *Micrococcus tetragenus.*

Terminal Infections.—This term is applied to those secondary infections which so frequently occur in incurable conditions, especially chronic diseases of the heart, liver and kidneys, and are the immediate cause of death. Flexner has made an extensive study of such infections. In a series of 793 autopsies he found 255 cases of chronic heart or kidney disease, in 213 of which either a local or a general infection or both existed; of these, 52 were examples of general infection. In some the point of entrance of the bacteria was evident, in others it could not be demonstrated. The organisms found were, in the order of their frequency, *Streptococcus pyogenes, Micrococcus lanceolatus,* the *Staphylococcus pyogenes aureus, B. aërogenes capsulatus, B. coli, Micrococcus gonorrhœæ, B. anthracis,* and *B. proteus.* Pearce in a study of pneumococcus infections found bronchopneumonia, frequently accompanied by a general pneumococcus infection, to be a common cause of death in chronic renal and cardiac disease; and less frequently in leukæmia, general sarcomatosis and chronic tuberculosis. "It is perhaps safe to say that the majority of cases of advanced arteriosclerosis and of Bright's disease succumb to these intercurrent infections" (Osler). The same holds true for many other chronic diseases. Flexner, acting upon the supposition that the tendency to general infection was due to a diminished bactericidal power of the blood, carried out a series of investigations with the blood serum of persons suffering from advanced chronic diseases and found it to be less destructive to the *Staphylococcus pyogenes aureus* than the serum of healthy individuals. More recently Longcope has demonstrated that a decrease in the bacteriolytic complement of the blood occurs in such cases.

The Value of Bacteriological Examination of the Blood.—It is evident from the preceding summary that the bacteriological examination of the blood during life gives results not only of scientific importance but also of great value in diagnosis, prognosis and treatment. Every clinician recognizes a group of diseases, with or without local lesions and etiologically independent, which present common symptoms characterized as "septic," *e. g.*, endocarditis and general miliary tuberculosis. These general symptoms may be due to toxæmia but in many a bacteriæmia exists and an examination of the blood may establish an etiological diagnosis. For a rational study of serum therapy such a diagnosis is essential, as has been emphasized by Marmorek and Hektoen.

Some very striking examples of this form of diagnosis have been reported. Perhaps the most important is the differentiation of typhoid-like diseases and our recently acquired knowledge of paratyphoid infections. Not a few cases of pneumococcæmia, and other forms of bacteriæmia, without localization, have been differentiated by blood cultures. In typhoid fever, the bacilli occur in the blood so early that a positive diagnosis may be made by blood culture before the clinical picture is distinct and before a positive Widal can be obtained.

Concerning the usual forms of general infection in surgical practice, Ewing concludes as follows: "In the great majority of cases of local or general septic infections, septicopyæmia, septicæmia, pyæmia, diffuse suppuration, osteomyelitis, etc., bacteria are present in the circulating blood *only for short periods and at infrequent intervals, most frequently during chills.* A few hours before death from septic infection, various bacteria, some of which may not be active in the original process, make their way into the circulation. In a very moderate number of cases of septic infection, especially those which are not attended by local abscess formation, the bacterial agent may be isolated from the blood during the progress of the disease."

Cabot believes that the literature, which indicates positive results in 33 per cent. of the cases, gives altogether too favorable an impression of the value of blood cultures in sepsis. This opinion is shared by DaCosta.

The Technique of the Bacteriological Examination of the Blood.—The following description by Hektoen covers all important points:

"The best method to secure blood for bacteriological cultures is venous punctures under the most scrupulous asepsis. Naturally, glass syringes are preferable to metallic because more easily sterilized and because transparent. The skin must be scrubbed carefully and prepared as customary for surgical operations. By some it is regarded as sufficiently cleansing to wash the area about the puncture with alcohol or ether. In practically all cases one of the veins at the elbow, usually the median, is selected for the puncture, and a moderate constriction of the arm will distend them so that in most persons they are made clearly visible and palpable. In fleshy persons it may be found impossible sometimes to make apparent in this way the location of veins, in which case it may be necessary to make the puncture more or less blindly. The discomfort is insignificant, and when properly done with a sterile needle, it is without danger.

Various procedures have been used to secure blood for bacteriological purposes, but real progress has followed only the use of venous puncture and its simplicity and certainty recommends it above all others. Ordinary cutaneous puncture is quite worthless for bacteriological purposes because of the small amount of blood obtainable and especially on account of the frequency of contamination.

Immediately on withdrawal of the needle after filling the syringe suitable media should be inoculated with the blood before clotting takes place. In most cases it will probably be deemed most advantageous to inoculate small quantities of the blood, *e. g.*, 1 cc. into large quantities of some liquid medium like bouillon, *e.g.*, 100 cc. The main reason for this dilution is the necessity to overcome, as far as possible, the natural bactericidal properties of blood, at least for some bacteria. In order to increase the chances for positive results the number of flasks inoculated may be multiplied to almost any practicable number. Gonococci and other organisms require special methods.

To obtain some idea of the number of bacteria in the blood it will be necessary to employ the plate method. This has been used with excellent results by Schottmüller in the study of typhoid fever. He has found that the mixing of 2 to 3 cc. of blood with 6 cc. of agar gives sufficient dilution. In the plates thus made the number of colonies developing may be counted and the bacterial content of the blood estimated from time to time.

Anaërobic methods may be used when it is deemed advisable, but so far no extensive systematic studies of the blood seem to have been made by such methods. Gwyn and Cole have isolated *B. aërogenes capsulatus* from the blood during life.

During the process of inoculating flasks, or tubes of solid media, great care must be taken to prevent aërial contamination. The mouth of the uncorked flask should be held in such a way that bacteria cannot fall into the medium. It is to be remembered that one single coccus, for instance, is sufficient to cause contamination of a flask. The most dangerous sources of contamination are the skin of the patient and the air. Undoubtedly organisms sometimes are picked up from the deeper layers of the skin as the needle passes through. In most instances the contaminating organisms will be found to be vulgar staphylococci and it will be a safe rule to place no significance on the development of growths of staphylococci, especially other than *Staphylococcus pyogenes aureus*, in cultures from the blood, except under very special conditions. From time to time the finding of ordinary staphylococci in blood cultures have led to the misleading announcement that the cause of certain diseases of unknown etiology has been discovered.

The inoculated flasks are then placed in the incubator for twenty-four to forty-eight hours, when they are examined for turbidity and other evidences of bacterial growth. When the bouillon remains sterile the blood corpuscles fall to the bottom intact, the supernatant fluid becoming clear, or nearly so. In the case of streptococci a frequent early evidence of growth is diffusion of hæmoglobin, *i. e.*, laking of the blood owing to the development of a special hæmolytic substance produced by streptococci. This substance has been studied especially by Besredka, and is called by him streptocolysin. Ordinary bouillon is sufficiently isotonic with human red corpuscles, so that they may remain quite intact in it for days in the absence of bacteria. In case litmus milk has been used as the medium, the growth of pneumococci, for example, may be signalized by redness and coagulation. Typhoid bacilli usually cause a diffuse turbidity of bouillon in twenty-four to forty-eight hours. In order to secure easily sufficient material for microscopic examination and for subcultures from flasks of blood cultures the use of long sterile pipettes is very convenient. During these manipulations there is always danger of accidental contamination unless great care is used.

The bacteriological examination of the blood during life requires at least ordinary, careful bacteriological training and fairly complete laboratory facilities. There is nothing about the method that necessitates any extraordinary skill; the most important part is conscientious regard for fundamental bacteriological principles, so as to escape contamination and erroneous conclusions."

Pathology.—Toxæmia and Septicæmia.—With any given organism the general pathological picture is the same whether that organism produces a toxæmia or a septicæmia, for the lesions in either condition are due to the dissemination of the soluble chemical substances elaborated by the infecting microörganisms and it matters little whether the latter remain in a localized lesion or circulate freely in the blood. It is therefore impossible to distinguish, except perhaps in degree, between the lesions due to septicæmia and those due to toxæmia. The character of these lesions varies, however, according to the character of the infecting organism. As the bacterial

products are soluble and by means of the blood and lymph circulations reach all parts of the body, so are the changes caused by them, as a rule, equally widespread. On the other hand some toxins exhibit an affinity for certain types of cells, as the tetanus toxin for those of the central nervous system; or they have a definite relation to certain cells, as that of the toxin of typhoid bacillus to endothelial cells. It is therefore possible to distinguish to some extent between the general effects produced in common by most toxins and the special, often specific, action of any given toxin.

The theory that bacteria may mechanically produce local disturbances has gradually lost its force as the result of a more thorough knowledge of the bacterial products and the mechanism of intoxication. The *B. anthracis*, which, because its toxin could not readily be demonstrated, was long supposed to have a mechanical action, has recently been found by Vaughan to possess an intracellular toxin. It is doubtful if any of the pathogenic microörganisms are devoid of the power of producing toxic substances. The thrombi of microörganisms, long considered as a manifestation of mechanical action, are to be regarded as the result of a multiplication occurring after, or perhaps during, the few hours preceding, death. Such thrombi are without associated lesions and are seldom found either after experimental inoculation or in man when the autopsy is made immediately after death; secondary suppuration about such thrombi transfers the condition to the group of pyæmias.

Gross Changes.—The bodies of those dying from severe septicæmia present little or no rigor mortis; the rigidity comes on early and soon disappears. Decomposition begins early and advances rapidly. In infection with gas-forming organisms local or general emphysematous infiltration may be present. The blood does not clot readily and discoloration of dependent parts is usually well marked. The lining of the heart, larger vessels, and the serous cavities, may be stained by hæmoglobin, and occasionally the fluids of the pericardium and other cavities may also be discolored from a similar cause. Small petechial hemorrhages may occasionally be seen beneath the skin, the serous membranes, especially pleura or pericardium, and less frequently within the substance of various organs. In the intestine, hyperæmia with either petechial or diffuse hemorrhage may occur. The minute hemorrhages in these locations are more frequently found in pyæmia and are supposed to represent extravasation about minute emboli; they are especially associated with malignant endocarditis. In some cases, however, distinct changes in the vessel wall are found (Howard), and it is possible that these may be due to an endotheliolytic substance of bacterial origin. Occasionally the hemorrhages are so numerous as to justify the term hemorrhagic septicæmia. Several attempts have been made to demonstrate bacteria in direct relation to those lesions, but the results are contradictory.

The spleen, in most cases, is more or less swollen, deeply congested and of lessened consistence, and at times semidiffluent. The capsule in acute cases is tense and on incision retracts, allowing the softened dark-red pulp to protrude. On section the Malpighian bodies are more or less obscured by the increase of pulp and occasionally cannot be recognized. In other cases although the organ is swollen, its substance is quite firm, and the Malpighian bodies appear as greatly enlarged grayish bodies. If seen after the height of the process the spleen may be soft and lax with a wrinkled capsule, the

result of volume lost in the subsidence of the congestion and the diminution of the pulp.

The heart, liver and kidneys present the characteristic appearance due to cloudy swelling and fatty transformation, though this appearance is often obscured by an intense congestion. Œdema of the kidney is not unusual and small hemorrhages may be present in all these organs. True hemorrhagic nephritis is a rare complication. The lymph nodes are usually swollen, congested and œdematous. Congestion and œdema of the lung, with or without bronchitis, is quite constant, and not infrequently irregular areas of lax pneumonia are found.

In those cases—the so-called cryptogenetic infections—in which a local lesion was not discovered during life it may be found at autopsy in the genito-urinary, gastro-intestinal or respiratory systems, or perhaps in an inflammation of the middle ear or in an obscure bone lesion; on the other hand no portal of entry may be discovered.

Histology.—This includes a study of the lesions observed in man and of the experimental intoxications in animals. The conclusions herein given are based principally upon Flexner's study of toxalbumin intoxications, the studies by Councilman, Mallory and Pearce of diphtheria, Mallory's investigation of typhoid fever, and the studies by Homén and his associates of streptococcus infection.

The lesions of which we know the most are those of diphtheria, because the changes can be studied, not only in the human individual suffering from the disease but also in animals by utilizing the very definite toxin of diphtheria. The first complete study of the general lesions in diphtheria was made by Oertel who demonstrated that the most constant and widespread lesion is a hyperplasia of certain cellular elements, followed later by focal areas of necrosis. This is best seen in the spleen and lymph nodes. The cells which proliferate are as a rule endothelial and have those characteristics best described by the term epithelioid. These cells possess a low grade of phagocytic power.

Councilman, Mallory and Pearce have shown that the distinctive lesions of diphtheria are the result of proliferation, phagocytosis and degeneration. The proliferation of the endothelial cells gives rise to an accumulation of cells not unlike the epithelioid cells of tubercle. These engulf and destroy the lymphoid cells, thus explaining in part the nuclear fragmentation which in part, also, is due to necrosis of the large cells themselves. These lesions are due solely to the toxic substance brought to the lymph node. These investigators emphasize also the presence of large numbers of plasma cells in the spleen.

All toxins have more or less power to produce degenerative lesions as cloudy swelling or fatty metamorphosis in the liver; small hemorrhages and infiltration of lymphoid cells are also not infrequent. In diphtheria and typhoid fever, and less frequently in scarlet fever, minute necroses usually spoken of as focal necrosis may occur. These necroses both Flexner and Reed, as the result of experimental investigations, consider to be due to the direct action of toxic substances. Mallory, on the other hand, explains them by the formation of small emboli of endothelial cells. Flexner presupposes an injury to the wall of the vessel allowing transudation to take place. Councilman, Mallory and Pearce describe two forms of necrosis in diphtheria, one about the central vein, and the other in the form of dissemi-

nated nodules. They are inclined to regard both as due to capillary obstruction plus the action of a toxic substance.

The heart in all forms of intoxication, is the seat of cloudy swelling or fatty change. In some diseases, however, as diphtheria, hyaline degeneration with vacuolization of the fibers and changes in the interstitial tissue are not infrequent. The interstitial changes may consist of a focal accumulation of plasma and lymphoid cells, thus constituting a true acute interstitial myocarditis which may occur independently of degenerative changes in the muscles; or, on the other hand, of a true proliferation of the connective tissue elements secondary to degeneration of the muscle and therefore analogous to fibrous myocarditis. From the work of Thomas it is evident also that the heart lesions, in diphtheria at least, may be due to a fatty degeneration of the peripheral nerves. The heart in typhoid fever, scarlet fever and diphtheria has been thoroughly studied by Romberg, who emphasizes the frequency of interstitial changes, especially in diphtheria. He believes many of the cases of fibrous myocarditis to be the result of such an interstitial condition occurring in the course of acute infectious diseases. Romberg has also described in connection with the nerves of the heart a round cell infiltration of the connective tissue sheaths.

The kidneys, like the heart and liver, are commonly the seat of cloudy swelling or fatty transformation. These changes are most evident in the cells of the convoluted tubules which may also occasionally undergo hyaline degeneration. In other cases exudative and hemorrhagic lesions, involving especially the glomeruli, may be found; or an irregular infiltration of the interstitial tissue with lymphoid and plasma cells. This last lesion has been especially described by Councilman in connection with diphtheria, and its occurrence in scarlet fever has been noted by Pearce. In scarlet fever, and less frequently in pneumonia, proliferative changes in the glomeruli may occur. These may involve the cells of the capillary tuft (capillary glomerulitis) or the cells lining the capsule of Bowman (capsular glomerulitis). Hyaline thrombi may be found in a variety of intoxications in the capillaries of the glomeruli.

The most comprehensive study of the lesions due to the streptococcus toxin is that by Homén and his pupils. In the nervous system was found a diffuse granular degeneration followed by slight necrosis and the immigration of leukocytes. Proliferation of the endoneurium and of the nerve sheaths was also evident. The lesion in the liver consisted of degenerative changes with small areas of necrosis and a tendency to the formation of connective tissue. The lungs showed a low grade of desquamation of alveolar epithelium, exudation of serum and immigration of leukocytes; a continued administration of toxin caused the formation of connective tissue. The early changes in the heart muscle were those of parenchymatous degeneration; in the latter stages, interstitial changes were sometimes seen. The kidneys showed parenchymatous changes but no nephritis or cell accumulations. In the course of their investigations they observed that the streptococcus stimulated the phagocytic powers of the leukocytes and endothelial cells. This phagocytosis in streptococcus infection has recently been emphasized by Ruediger.

All toxic substances act upon the individual cell. The character of the change in the cell depends upon the nature of the toxic agent and upon the resistance of the cell. The lesions produced by toxins have been very well

summarized by Mallory as follows: "The effects which injurious agents, especially the toxins, secreted by bacteria, produce on tissues are manifested in four different ways: (1) by degeneration or necrosis of cells, (2) by exudation from the bloodvessels, (3) by proliferation of cells, (4) by phagocytosis." Mallory believes that strong toxins cause degeneration or necrosis of cells, and exudation, while dilute and weak toxins produce proliferation and phagocytosis. As types of the first group he cites the toxin of the *Staphylococcus pyogenes aureus* and that of the *Bacillus diphtheriæ;* the best example of the second group is that of the *Bacillus typhosus.* Strong toxins, however, can produce the same processes of proliferation and phagocytosis when sufficiently dilute. This is illustrated perfectly by comparing the local lesions due to the diphtheria toxin with those occurring in the internal organs.

In the same way some organisms, as the typhoid and tubercle bacilli, which ordinarily produce a mild toxin and cause proliferation, may, especially when the organisms are massed in large numbers, produce a concentrated toxin capable of causing necrosis and purulent exudation. Phagocytosis is most frequent in those infections in which a mild toxin is formed as in typhoid fever, although it may occur to a limited extent under other conditions.

Pathology of Pyæmia.—Any pyogenetic microörganism capable of existence in the blood stream may cause pyæmia. Those most frequently found are the staphylococcus and the streptococcus, less frequently the pneumococcus, the gonococcus and the typhoid bacillus; other forms have been found occasionally. In considering the pathology of pyæmia it is necessary to discuss the manner in which the microörganisms enter the blood stream and the conditions which determine the secondary localization in the various organs. In the majority of local infections followed by pyæmia the invasion of the blood is not direct, by the passage of the organism through the vessel wall, but indirect as a result of an involvement of the vessel, usually a vein, in the inflammatory process and the consequent formation of thrombi. From these infected thrombi small particles containing bacteria pass into the general circulation and, reaching vessels too small to allow their passage, become impacted. Whereas a bland embolus would cause a simple infarction, these infected emboli, through the microörganisms which they contain, cause local suppuration. A somewhat similar mechanism is seen in malignant endocarditis; small fragments of the exudate or of the thrombotic masses on the valve are swept into the blood stream and cause, upon impaction, embolic abscesses.

Not only in man, but also in experimental studies upon animals, it is seen that pyæmic abscesses develop much more readily when the cocci are adherent to some inert substance capable of mechanically plugging the smaller vessels. Thus Ribbert in his classical experiments found that the injection of cultures of the *Staphylococcus aureus* seldom caused abscesses in other organs than the kidney. When, however, he injected cultures scraped from potato, with small particles of the potato substance adherent, a localization occurred in other organs; indeed, various grades of pyæmia could be produced by varying the size of the potato scrapings. Similar results were obtained by Pawlowsky with simultaneous injections of cinnabar and the organism.

Occasional cases occur, however, in which the emboli do not contain portions of blood clot but are composed of microörganisms only. Such,

possibly, may originate by slow growth in lymphatic vessels and enter the blood stream as definite colonies or clumps which are finally arrested in the capillaries. Rarely, as in the case cited by v. Kahlden, a thoracic duct involved in an acute abdominal inflammation may be the point of origin of emboli. Such dissemination is analogous to that occasionally occurring in connection with tuberculosis and cancer involving the thoracic duct. Again it is possible that single organisms may find foci of altered or injured tissue favorable to their multiplication. This question of *locus minoris resistentiæ* is illustrated in the experimental production of endocarditis and osteomyelitis. The former can readily be produced if the valve is mechanically injured before injecting the microörganisms into the blood stream; the latter if a bone is first fractured. Further illustration is afforded by the experimental study of Cheesman and Meltzer, who found that by mechanically injuring various tissues they could cause bacteria circulating in the blood to settle in any place they might select.

It is evident therefore that while embolism is an important factor in the production of pyæmia, it is not essential in all cases. Some writers, however, and especially Watson Cheyne, insist that embolism is necessary to the production of true pyæmia, and prefer to apply to the condition frequently called "chronic pyæmia," due to abscess formation in injured tissues, the term "multiple abscesses." This distinction would appear to be unjustifiable in view of the commonly accepted definition of pyæmia—septicæmia with multiple secondary abscesses. Indeed, it is evident from our general knowledge of the conditions leading to inflammation that the local injury is the essential condition; and that even with an infective embolus it is probable that inflammation does not begin until the surrounding tissue has been rendered less resistant by an ischæmia, the mechanical result of the occlusion of the vessel.

The site of the secondary localization depends largely on the portal of infection. In inflammations accompanied by thrombophlebitis the emboli are usually arrested in the lungs, though an open foramen ovale may allow the passage of large masses to the arterial system; or minute emboli capable of passing through the capillaries of the lung may reach the general system. Localization in the territory of the general circulation may result also from emboli arising in a secondary phlebitis in the neighborhood of pulmonary abscesses or from similar masses set free from a malignant endocarditis. Under these circumstances the kidney, spleen, brain, heart and voluntary muscles are the more common seats of secondary suppuration; less frequently the liver, serous membranes, joints, skin, or eye may be involved.

The changes which occur in the tissues about the infective material are those characteristic of abscesses in general: A central mass of microorganisms surrounded by a zone of necrosis, an outer zone of leukocytic infiltration and between this and the normal structures, granulation tissue. Naturally, the various degenerative changes affecting the parenchymatous organs in toxæmia and septicæmia are present also in pyæmia.

Portal Pyæmia.—An unusual form of pyæmia is that in which, as the result of a local infection in the portal system, multiple abscesses occur in the liver with or without general suppurative pylephlebitis. It may arise as the result of inflammatory lesions of the stomach, intestine, or gall bladder, or, rarely in the new-born in connection with a phlebitis of the umbilical vein. Appendicitis is perhaps the most frequent cause.

Symptoms.—Toxæmia.—We distinguish certain general symptoms common to all forms of toxæmia, as fever, rigor, general malaise, prostration, rapid pulse, headache and restlessness; and frequently certain special symptoms peculiar to the toxin of the infecting organism. These special symptoms usually constitute the characteristic clinical picture in certain diseases, as in tetanus, diphtheria and typhoid fever.

The toxæmia accompanying suppurations, the so-called sapræmia, due to the *Staphylococcus aureus* or the streptococcus, may come on gradually with slight chills, a low irregular fever reaching 100° to 102° F., loss of appetite, sleeplessness and a general condition of restlessness. These symptoms usually subside promptly after local treatment. At other times it comes on abruptly, the symptoms reaching their height within twenty-four hours. This happens most frequently when a hitherto localized lesion suddenly and rapidly involves other tissue, and is to be explained by the freeing of a large amount of toxin which, passing into the lymphatics, quickly reaches the blood stream. The same rapid onset may be seen in a rapidly developing virulent infection of a previously clean wound. The onset is usually, but not invariably, marked by a rigor and a sudden rise of temperature to 103°, 104° F. or even higher. The rigor may be slight or severe and may or may not recur. The usual concomitants of fever, the hot, dry and flushed skin, thirst, headache, and coating of the tongue are seen. Vomiting is usual and may persist; the pulse is rapid and full; the respiration hurried; the urine scanty and high colored. As the intoxication continues, general weakness, frequently to the extent of prostration, develops; at other times the patient becomes restless, anxious and irritable. In neglected cases or those in which the source of the intoxication cannot be removed, the prostration becomes extreme and tremors due to muscular weakness develop. A delirium, noisy or of the low muttering type, may become constant, but occurs usually only at night. The tongue becomes dry and brown, mucous accumulates in the eyes, the lips are covered with sordes, diarrhœa occurs, and the fæces and urine are passed unconsciously. The skin may be jaundiced or show petechial hemorrhages. This stage may gradually pass into coma, and, with a falling or subnormal temperature, end in death on the third or fourth day after initial symptoms. Other cases continue in a distinctly "typhoid" condition and die from exhaustion after a longer period. The urine may contain albumin and occasionally a few hyaline casts; in severe cases an acute exudative nephritis may develop.

Septicæmia.—The symptoms of septicæmia are due to the same cause—an intoxication—as are those of toxæmia and therefore are similar in character, though usually more severe. The initial rigors are more marked and frequently persist. The temperature remains constantly higher (103° to 105° F.), but with daily remissions or even intermissions. The anorexia is more profound, as is also the "typhoidal" condition, when it occurs. Jaundice is more frequent and of severe grade. Capillary hemorrhages are not uncommon. The character of the symptoms differs naturally according to the infecting organism.

Pyæmia.—This condition, preceded as it is by toxæmia and septicæmia, has no distinctive symptoms except those due to the secondary suppurative foci, and these are not always conspicuous. The onset is marked by a severe initial rigor and a rapid rise of temperature to 103° or 105° F. These rigors, followed by fever and sweating, occur at intervals of every day, or

every other day, and may frequently have more or less periodicity. The constitutional symptoms are similar in character to those of septicæmia but are exceedingly severe. The signs are dependent on the site of the secondary suppuration. Thus cough and dyspnœa point to an involvement of the lung which physical examination may confirm; if the abscess is near the surface of the lung the clinical picture of pleuritis may develop. Pleuritis may also be a manifestation of pyæmia independently of previous lung involvement. In a similar way the peritoneum, the pericardium, the joints, and the meninges may be involved. Abscesses of the kidney may be recognized by pain and tenderness in the lumbar region and albumin or occasionally blood and pus in the urine; an enlarged tender spleen is suggestive of the changes following embolism of that organ. Very important lesions may occur in the eye. The central artery of the retina may be plugged by an embolus, causing sudden loss of vision in the affected eye and later, through the microörganisms present in the embolus, a panophthalmitis may develop. This last condition may be caused also by an embolus lodging in the ciliary region or iris. Occasionally abscesses of the subcutaneous tissues, or of superficial organs, as the thyroid, salivary glands, or testicle, may be present.

Cardiac murmurs are usually heard, and although often functional the possibility of an acute endocarditis must be considered. The skin is often of a yellow tinge, and occasionally in severe cases distinctly jaundiced (hæmatogenous icterus). An erythematous rash of the scarlatina type, but differing in its distribution, is not infrequent. Very rarely a pustular eruption is seen, and in the later stages of the disease petechial or even diffuse hemorrhages. These hemorrhagic lesions are more frequent in cases with endocarditis.

Death usually occurs in the second week, though a few cases run into the third week. The fatal result may be due directly to any one of the secondary lesions of the heart, lung, brain, or meninges, or the patient may pass into a "typhoid" state and die of exhaustion with or without coma. In rare cases death may occur suddenly from impaction of a large embolus in the pulmonary artery, or from cardiac or cerebral embolism.

The so-called chronic pyæmia is characterized by the formation of fewer abscesses, a milder course and longer duration. Acute symptoms, as rigor, fever and pain, occur with each localization and then subside. The secondary lesions are usually in the joints or subcutaneous tissues. The disease may last for months, but its course is usually progressively downward, with fatal termination.

Changes in the Blood.—Only those alterations accompanying infection by the common pyogenic microörganisms will be discussed here.

Red Cells.—In milder forms of toxæmia due to this group of organisms only slight changes in the blood may be evident, but all observers agree that in severe cases a very marked anæmia is present. Ewing states that "in no other disease do the red cells suffer destruction so constantly and to such an extent." The average loss of red cells is from 200,000 to 1,000,000 per week and the diminution persists as long as the infection continues. The anæmia varies according to the character of the case, the most marked anæmia being associated with uterine sepsis. Hayem reports a case of puerperal sepsis with only 1,450,000 red cells per cmm. and 20 per cent. of hæmoglobin; Cabot, a suppurating fibroid of the uterus with 1,800,000;

Ewing, a septic endometritis, not puerperal, with 1,600,000 red blood cells and 20 per cent. hæmoglobin; while Grawitz, in a case of intensely acute puerperal sepsis with profuse bleeding, found but 300,000 red cells. Cabot gives as the average count for puerperal septicæmia, 3,500,000. Nucleated and distorted red cells may occasionally be seen in the second or third week of severe septicæmias. The loss of hæmoglobin is one of the chief alterations and is usually in proportion to the loss of red cells. This solution of hæmoglobin may lead to distinct hæmoglobinæmia, causing staining of the body fluids and tissues, jaundice of the skin and, as mentioned by Ewing, microscopic appearances in the internal organs similar to those of pernicious malaria. Our recently acquired knowledge of bacterial hæmolysins would appear to explain in part this destruction. An increased tendency to crystalization of the hæmoglobin has been observed. In severe cases a very rapid diminution in the specific gravity of the blood may be found.

Leukocytes.—The character of the leukocytosis depends upon the severity of the infection, the resistance of the individual, and to a less extent on the character of the local lesion. If the latter is a distinctly purulent condition a higher leukocytosis may be expected than in conditions accompanied by fluid exudate; on the other hand encapsulated pus may not cause a leukocytosis. If the infection is severe and the resistance good a marked increase in leukocytes is the rule; on the other hand, if the resistance to a severe infection is poor, there may be no leukocytosis, or even leukopenia. This may be seen not infrequently in puerperal septicæmia or other severe streptococcus infections which completely overwhelm the reactive power of the organism. Also mild cases may occur with slight or no leukocytosis. The leukocytosis is of the ordinary polymorphonuclear type with diminution or no change in the number of eosinophiles and lymphocytes.

Iodophilia.—Locke and Cabot have reached the conclusion that this reaction is characteristic of toxæmic conditions and especially of those associated with suppuration. The test is simple. A blood film prepared in the ordinary way is pressed down on a drop of iodine solution[1] on a glass slide and examined with an oil immersion lens. Normal neutrophiles are stained a bright yellow; but in septicæmia and certain other conditions reddish-brown granules or a diffuse brownish coloration is seen. Free extracellular bodies may also react, but they are of no diagnostic value. The presence of the bodies within the cells is always pathological; they have never been seen in normal blood. In general the intensity of the reaction appears to indicate the severity and duration of the local process and the amount of septic absorption. Of great importance in connection with virulent infections is the occurrence of a marked iodine reaction without leukocytic reaction. In these cases it is a valuable control of conclusions based on the blood count only. As a toxæmia clears up after free drainage of pus so do the granulations in the leukocyte rapidly disappear. Persistance of the reaction indicates incomplete drainage. Of this test Cabot says: "The iodine reaction, like the leukocyte reaction, usually means septicæmia, but not always pus. It is present in cases of grave anæmia, and in a variety of toxic and infectious conditions (malaria, uræmia, grave anæmia, carbon monoxide poisoning, etc.), some of which produce leukocytosis, while others do not. Its value consists

[1] Iodine ..... 1 gram
Potassium iodide ..... 3 grams
Water ..... 100 cc.
Gum arabic ..... 50 grams

in the fact that it adds another to our list of clinical indications of the presence of toxæmia—such indications as pyrexia, tachycardia, albumosuria and leukocytosis. None of these is present in every case and any of them may be present when toxæmia is absent. Hence the addition of an independent indicator like iodophilia to our list strengthens our diagnostic resources considerably."

Portal Pyæmia.—Portal pyæmia or suppurative pylephlebitis offers certain special symptoms. The liver usually increases rapidly in size and this enlargement is accompanied by intense pain in the right hypochondrium and tenderness on palpation. Gastro-intestinal symptoms are prominent, usually with vomiting. Large abscesses pressing on the portal vein may cause ascites, and a similar pressure on the large bile ducts, jaundice; these symptoms, however, are not constant. Peritonitis, resulting from rupture of an abscess on the surface of the liver, or by direct extension, may complicate the picture. Exploratory puncture may occasionally demonstrate an abscess and settle the diagnosis. The course of the disease is severe and rapidly fatal.

Diagnosis.—When the general symptoms described in the preceding paragraphs occur in connection with a local suppurative or gangrenous lesion (dissection, autopsy, or other wound, post-partum endometritis, osteomyelitis, otitis media, or local inflammation after operation), and especially if the primary inflammatory condition is a rapidly progressive one, the attendant must attempt to distinguish between a toxæmia and a septicæmia and to consider the possibility of pyæmia. The differentiation between the first two is difficult and almost impossible without the aid of blood cultures; while a diagnosis of pyæmia can be made only when the secondary localizations offer definite symptoms. If, after removal of the local infection, the general symptoms subside, it becomes evident that the trouble was an intoxication; if, however, they persist, a general septicæmia in all probability exists. This can be determined absolutely only by obtaining positive results in blood cultures; negative results leave the diagnosis still doubtful. Fortunately such differentiation is now not essential in deciding upon treatment; it must be remembered, however, that one can obtain no satisfactory knowledge of the value of the various forms of serumtherapy until a distinction is made not merely between toxæmia and bacteriæmia, but more important still between various types of bacteriæmia.

The surgeon can usually explain the occurrence of "septic" symptoms by an examination of his incision, the injured tissue, or whatever the local lesion may be. The physician, on the other hand, may be confronted with general symptoms, atypical or unusually severe, developing suddenly in the course of some definite clinical picture, and which he cannot explain. Or he may recognize a condition as septicæmia from the onset, with no local disease of any kind and without evident portal of infection. Such obscure conditions may be due to general infections with the pneumococcus, typhoid or paratyphoid bacillus, *B. pyocyaneus*, the gonococcus, or one of the common pyogenic cocci. In such cases the only means of exact diagnosis, in the early stages, is by a bacteriological examination of the blood.

The differentiation of pyæmia from other affection is often very difficult. Of prime importance is the recognition of the local infection. Obscure primary lesions as osteomyelitis and abscess of the genito-urinary or alimentary tract, are frequently not recognized. The differentiation from septi-

cæmia depends on the secondary manifestations. The diseases with which it is perhaps most frequently confounded are typhoid fever, acute miliary tuberculosis, malaria and malignant endocarditis.

Malignant endocarditis, in the broadest sense of our definition of pyæmia, is a pyæmic manifestation. It is a secondary condition, the result of a bacteriæmia of definite or unknown origin and is frequently accompanied by other suppurations. Moreover, through embolism it usually causes other abscesses. Suppurative arthritis following acute infectious diseases, as scarlet fever and gonorrhœa, are really mild forms of pyæmia usually differentiated clinically.

It should be remembered that pyæmia may rarely complicate almost any one of the infectious diseases, for suppuration is not due to any specific organism or group of organisms, but may be caused by a great variety of bacteria.

Prognosis.—This depends in toxæmia on the type of infection, the severity of the intoxication, and the resistance of the individual. In surgical and obstetrical infections the general symptoms usually subside promptly after proper treatment of the local lesion from which the toxic substances are absorbed. Streptococcus toxæmia is considered more serious than other forms. The resistance of the individual is an important factor, some persons resisting an intoxication to which old and debilitated subjects succumb. Local lesions which cannot be reached surgically, or those accompanied by thrombosis, always warrant a guarded prognosis because of the possibility of the development of septicæmia or pyæmia. The time which elapses before proper treatment is inaugurated has an important bearing on the result. In some diseases, as pneumonia, typhoid fever and diphtheria, in which the toxæmia may be out of all proportion to the fever and the extent of the local lesion, it is of serious prognostic import. Rugged individuals with moderate pneumonic solidification and pyrexia may quickly succumb to an overwhelming toxæmia.

Septicæmia, when absolutely diagnosed, has generally been considered almost hopeless. This has been true especially of streptococcæmia occurring either in surgical practice or in such diseases as diphtheria, scarlet fever and smallpox. The result of the bacteriological examination of the blood in a great variety of conditions indicates, however, that this view must be modified. Although no generalization concerning prognosis can yet be based on such examinations, there is very definite evidence that recovery may take place in various forms of bacteriæmia. Petruschky reports recovery from general infection with pyogenic cocci, as does also Bertelsmann, Libman and Hektoen. Jochmann reports a case of gonococcæmia which recovered.

Pneumococcæmia, according to Ewing's collection of cases, is usually fatal. He believes, however, that except as an occasional agonal invasion, this condition is rarely found in the absence of metastatic inflammations. Proschaska, on the other hand, found the organism in all of 50 cases and in varying types of the disease, and concludes that a general infection in pneumonia does not necessarily mean a grave prognosis. Fränkel believes the prognosis depends on the number of organisms found.

The surgical forms of pyæmia and those accompanied by ulcerative endocarditis, meningitis and suppurative pylephlebitis or extensive visceral abscesses are almost invariably fatal. The so-called chronic pyæmia and

the milder acute forms with suppuration in the joints, subcutaneous tissues, or other localities which may readily be treated surgically, frequently recover.

Treatment.—The treatment of the three conditions here considered is mainly surgical and therefore calls for but brief mention. All local suppuration, whether primary or secondary, if accessible should be evacuated and thoroughly cleaned and drained. Under such treatment a toxæmia usually subsides rapidly while a septicæmia or pyæmia is unchecked except in those rare instances in which the patient displays unusual powers of resistance. The general treatment seeks to stimulate this resistance and to conserve the strength of the individual. Nutritious and easily assimilated food in small amounts should be given at frequent intervals. Alcohol in the form of brandy or whisky is frequently given; strychnine may be of special value. The fever may be moderated by bathing. Quinine and the various coal tar products are of little value. Pain, vomiting, diarrhœa, and other symptomatic conditions, can be treated only as such. In short, the treatment is that of any continued fever—good nursing with attention to general hygienic principles and the treatment of symptoms.

Various attempts have been made to combat septicæmia and pyæmia by intravascular injections of formaldehyde and colloidal silver. The results obtained are, however, not sufficiently satisfactory to justify general use.

Sudden severe intoxication with collapse may justify heroic stimulation in the hope of supporting the patient until the excretion of the poison has begun. Under these circumstances the subcutaneous or intravenous injection of salt solution may aid very materially.

Serumtherapy.—The progress already made in the treatment of acute infections by immune sera offers some support for the hope that eventually each form of toxæmia or of septicæmia may be treated by a specific antitoxic or bactericidal serum. At present, however, successful serum treatment is practically limited to diphtheria. This is due in part to the differences in the chemistry of the bacteria and the manner in which toxins are secreted, and in part to differences in the mechanism of infection. The immune sera in the present state of our knowledge may be divided into (*a*) the antitoxic sera, (*b*) the bactericidal sera, and (*c*) those which are neither antitoxic nor bactericidal, or but slightly so, but which aid apparently by assisting the protective mechanism of the body. To the first group belong the antidiphtheria and antitetanus sera, each of which contains a true antitoxin for the soluble toxin of the diphtheria and tetanus bacillus respectively. The neutralization of the toxin by the antitoxin in each of these sera is apparently chemical in character and analogous to the neutralization of an acid by a base. Unfortunately for the success of the general treatment of toxæmia by antitoxic sera, the diphtheria and tetanus bacilli are the only important pathogenic organisms which produce soluble toxins; the toxins of other bacteria are closely bound to the mycoprotein and not readily separated from the cell. The direct antitoxic action of diphtheria and of tetanus serum is well known experimentally and that of the diphtheria serum clinically. Unfortunately the clinical use of tetanus serum is unsatisfactory owing to a peculiarity which the tetanus toxin has of uniting with the cells of the central nervous system. This union occurs early in the disease, is a very intimate one, and the poison when so bound to the cell is not at all, or but slightly, affected by the antitoxin. Technically expressed, these nerve

cells possess receptors for which the toxin has a special affinity, an affinity so great that the antitoxin cannot overcome it. For this reason tetanus antitoxin gives the best results when it is used early in the disease before the toxins are fixed or when intradural injection, which allows a less diluted antitoxin to come in intimate contact with the toxin-saturated cells, is practiced. The antitoxic sera have little or no bactericidal power.

The bactericidal immune sera are produced by immunization with those bacteria (typhoid, dysentery, cholera, etc.), which are usually described as possessing intracellular toxins in contradistinction to the soluble toxins of the diphtheria and tetanus bacilli. Such sera are not antitoxic or but slightly so. Their bactericidal power can readily be demonstrated experimentally, but when applied clinically so great an amount of serum must be employed that its use is impracticable. Moreover, owing to differences or irregularities in complement activity, the mechanism of bacteriolysis in man is not analogous to that in carefully planned experiments. When these problems are solved rational treatment of bacteriæmia may be expected.

The third group, but recently separated, includes the streptococcus, and possibly the staphylococcus and pneumococcus sera. These have no bactericidal power and are but slightly or not at all antitoxic. They act apparently either by stimulating certain cells (phagocytes) or by so altering the infecting organisms that they may readily be destroyed by these cells.

Antistaphylococcic sera may be dismissed with but brief comment. No serum satisfactory for clinical use has yet been prepared. Experimentally, a serum of but very slight protective power has been obtained. As a rule, even in large doses, it will not protect against more than twice the fatal dose, and quickly loses its protective power. It has been estimated that in combating human infection the average adult should require from 400 to 700 cc. of the serum.

Owing to the high fatality caused by the streptococcus and the frequency with which infection, either primary or secondary, occurs, much attention has been given to the preparation and mode of action of antistreptococcic sera. The first serum was announced by Marmorek, in 1895, but as yet the exact mode of action has not been demonstrated. This is due to a variety of conditions. We do not know whether we are dealing with one or with a variety of forms of streptococci; little is known of the streptococcus toxin; and until recently the mechanism of its toxic action and of the method by which the body resists this action have been little understood. Furthermore, in the clinical use of the serum the differentiation is seldom made between toxæmia and bacteriæmia, a point naturally of great importance in the interpretation of results.

Recently some light has been thrown on the mechanism of the protective action of antistreptococcic sera. The investigations of Bordet, Besredka and Ruediger, show that the leukocytes play an important role in combating streptococcus infections. These cells in the normal rabbit take up only non-virulent cocci; but in the rabbit receiving the antiserum they engulf virulent cocci also, and if the dose is not too large the animal recovers. In test-tube experiments the same phenomena are observed. It would appear at first glance that the antiserum stimulates the phagocytes. Further experiments, however, by Neufeld and Rimpau indicate that this is not so, but that some substance in the bacterial cell is neutralized by the antiserum, and after such neutralization the cocci do not resist ingestion by the leukocytes.

The substance destroyed by the serum, presumably a toxin, they suppose to be the agent naturally protective against phagocytosis.

That such an explanation of this mechanism is in all probability the proper one is indicated by the studies of Wright and Douglas confirmed by Hektoen and Ruediger, and others. These investigations, briefly summarized, show that the influence of the body fluids upon phagocytosis is not due to stimulation of the phagocytoses directly; but that certain substances (opsonins) in the fluids become attached to the bacteria, which, for some unknown reason, then become susceptible to phagocytosis.

Therapeutically, the use of antistreptococcic sera gives very contradictory results. Some of the most interesting results have been obtained in the treatment of scarlet fever. Baginsky, who believes that the streptococcus has an etiological relation to scarlet fever, used Aronson's serum on a series of 63 cases of scarlet fever; the doses varied up to 20 cc. The cases treated were severe and he found the serum to have a beneficial action. A close analysis of his figures shows a death-rate in injected cases of 11 per cent. and in uninjected of 17 per cent. The death-rate in his hospital for ten years had varied from 12 to 24 per cent. Aronson's serum is prepared by injecting horses with cultures rendered virulent by passage through animals. Moser, who holds that Aronson's method impairs the protective power of the serum against streptococci virulent for man, prepared a serum by injecting horses with cultures freshly obtained, usually from the heart's blood, of fatal cases of scarlet fever. As he has obtained nearly 30 different strains of the streptococcus and injects them all, his serum is polyvalent. Escherich uses this serum in all severe cases received at the Anna Kinderspital (Vienna). From November, 1900 to July, 1904, 1,069 cases of scarlet fever were admitted and of these 228 received serum. The mortality in the hospital prior to the serum treatment averaged 14.5 per cent; since, 8 per cent.; for the same period of time the general mortality from scarlet fever in other Vienna hospitals averaged 13.1 per cent. The dose employed varied up to 180 cc.; a second injection was rarely necessary. The effect of the serum on the clinical symptoms is noticed in a few hours; all symptoms are relieved without shock or collapse; the temperature falls to normal; the pulse and respiration improve and the nervous symptoms subside. For this effect, however, the serum must be given early, certainly before the height of the disease. No ill effects of the serum are noted, except the serum exanthem, which, however, never becomes a serious complication. With the same serum Bokay obtained similar results in a smaller number of cases.

The results obtained in the treatment of rheumatism, puerperal sepsis and various forms of secondary infection are contradictory.

A committee of the American Gynecological Society, in 1899, analyzed 351 cases of puerperal sepsis treated with antistreptococcus serum. The total mortality was 20.74 per cent. In 101 cases, in which a bacteriological examination was made, death occurred in 32.69 per cent.; in 251 without bacteriological control, in 15.85 per cent. The committee concluded that these results did not justify further use of the sera then available. Packard and Willson on the other hand collected, in 1902, 117 cases of streptococcus infection, including puerperal sepsis, erysipelas, pyæmia, local suppuration and secondary infection complicating tuberculosis, with a history of temporary improvement or complete recovery in 114.

The important points in treatment by antistreptococcus serum appear to be the following:

1. It must be demonstrated that the streptococcus is the organism responsible for the condition, or, if present with other bacteria, is the predominating pathogen.

2. The serum must be used early in the course of the disease; if general extension has taken place little or no beneficial result may be expected.

3. The first dose should be at least 20 to 30 cc. and if this does not produce a perceptible change in symptoms it should be repeated in twelve hours. If no relief follows such treatment it is useless to continue that particular serum and another brand should be tried. Injections should be made if necessary, every twenty-four hours.

4. The polyvalent sera appear to give more favorable results than those prepared with a single strain of streptococcus.

CHAPTER XXV.

ACUTE RHEUMATISM, OR RHEUMATIC FEVER.

By FREDERICK J. POYNTON, M.D., F.R.C.P. (Lond.).

Etiology.—*Acute rheumatism* takes a very prominent position among the diseases of temperate climates, and has from ancient times attracted much attention. No disease is more difficult to define, and of the more common diseases none has been more complicated by theories. For this reason the reader will possibly grasp the chief problems in the etiology the more easily if they are put in the form of a brief historical summary. It is at the present time especially necessary to devote particular attention to the views upon the causation, for upon the one to which he may incline will depend the physician's interpretation of the clinical facts of the disease and his line of treatment.

We frequently read in the early writings of a "rheum" or catarrh which flowed from the brain into the various regions of the body and caused pain and distress when it obtained a lodgment. This vague and indefinite conception has survived to the present day in a modified form, and often even now a vague ache or pain for lack of an accurate diagnosis is called "rheumatic." Early in the seventeenth century, however, the term rheumatism was used for a special form of arthritis, and distinguished from gout by a French physician, Baillou. Sydenham, in the *Observationem Medicarum*, also sharply differentiated these two diseases. There was again definite advance when in 1827 we read in Scudamore's writings accounts of cases of endocarditis and pericarditis arising from rheumatism, and find ten years later that Bouilland was so impressed with the frequency of the cardiac lesions that he grouped them as true rheumatic manifestations. From this time onward the belief has been slowly gaining ground that acute rheumatism is a systemic disease, and not only a form of arthritis. Nevertheless the continual use of the term articular rheumatism has greatly delayed this acceptance of the disease as a systemic one.

The next important landmark was gained by a study of rheumatic fever in childhood. Nearly two hundred years ago chorea was recognized as a sequela, and Botrel in 1850 held that all chorea was rheumatic in origin. In 1868 Hillier described the rheumatic nodule, and in 1888 Cheadle, in his Harveian lectures upon the manifestations of the rheumatic state in childhood and early life, conclusively demonstrated the widespread lesions of the disease. Even now, however, writings abound in which the conception of acute rheumatism is that it is an articular disease, and it will be evident from what follows that many of our difficulties are the outcome of this imperfect realization of the true meaning of acute rheumatism.

The tendency in recent years has certainly been to accept the view that it is a disease with numerous manifestations. It is, however, disputed whether there is one exciting cause or whether there are many, and this leads to a close consideration of the various factors in the etiology and of the various

views that have been put forward in explanation of the cause of acute rheumatism. Widely different theories have been elaborated. Cullen attributed rheumatism to the direct action of cold upon the joints, and looked upon it as essentially a local inflammation followed by a general fever. Later J. K. Mitchell influenced medical thought by his remarkable observations upon arthritis produced by nervous lesions. Exposure and chill were, according to this theory, believed to cause an irritation of the cutaneous sensory nerve fibers over a wide area, and thus to set up a central disturbance in the spinal cord and medulla oblongata. This disturbance was transmitted to the nerves of the various organs and tissues which were implicated by acute rheumatism and caused in turn the various manifestations.

The chemical theories of the causation opened up further paths for investigation, although none of them can claim to be satisfactory. The suggestion that the poison which caused the symptoms was lactic acid is the one most widely known, and was the most widely accepted. Yet the basis of fact upon which it rests is very slender. B. Richardson and Rauch produced endocarditis, pericarditis, and polyarthritis, by injecting a 10 per cent. lactic acid solution into the peritoneal cavity of dogs; but other investigators failed to confirm these observations, and the proofs of the occurrence of lactic acid in any excess in the tissues in acute rheumatism are entirely wanting. The view held by Latham and Haig, that uric acid is of first importance in the production of the disease, needs the support of clear demonstration. There is in fact no agreement upon the subject that uric acid is in excess in the blood, tissues, or sweat secretion of rheumatic fever.

When on the other hand, we investigate the reasons for looking upon acute rheumatism as infective, we find the most convincing evidence in every direction. To quote Dr. Cheadle's words upon this point: "The occasional epidemic prevalence, the variability of type, the incidence upon the young, the occurrence of tonsillitis, of endocarditis, of pneumonia, of erythematous eruptions; the rapid anæmia, the tendency to capillary hemorrhage and albuminuria; the implication of the joints, the relapses, the occasional supervention of hyperpyrexia, the nervous disturbance, the specific power of salicylic acid, are all suggestive of an infectious disease." The pathological and bacteriological facts in support of this view are also most convincing.

The exact nature of the infection, however, has led to much controversy, and at the present time there is no general agreement upon this point. The view that it is an infection akin to malaria can be dismissed. This is associated with the names of Saunders, M. Bertholon, and Maclagan, and was suggested by the idea that damp was in both diseases a powerful agent in the causation. The proof of the cause of malaria has disproved the relationship of the two diseases, and a study of the morbid anatomy of acute rheumatism points to its classification among the diseases that result from micrococcal infections; that is to say, with the diseases that result from infections with the streptococci, staphylococci and pneumococci.

With the dismissal of the malarial theory the present position is reached, and the several views upon it are as follows: (1) That there is no specific microörganism, but the disease is a form of septicæmia which owes its origin to staphylococcal or streptococcal infections. (2) That the disease is due to a specific bacillus. (3) That the microörganism is a diplococcus. (4) That the exciting cause is as yet unknown.

The second of these views, which looks upon the disease as the result of an infection with a specific bacillus, is not substantiated. A large bacillus had indeed been found by Achalme, in 1891, and later by other French observers, in fatal cases of rheumatic fever, and they held that it was the actual cause of the disease. Subsequent investigations have failed to confirm these results, and it seems impossible to believe that the bacillus, which was described as of a size equal to that of the anthrax bacillus, can have been overlooked by many observers. On the other hand, the investigations which point to a micrococcus as the exciting cause of acute rheumatism are very numerous and some are so complete as to carry great weight. Yet in their interpretation difficulties arise, for although it is accepted by most authorities that acute rheumatism is a systemic disease, there is no general agreement that it has only one exciting cause. On the contrary, there are many who maintain that different infective agents of the micrococcal group may produce acute rheumatism.

No value can be attached to the statement, commonly made, that rheumatism is a form of septicæmia. Any infection, if sufficiently severe, will cause a septicæmia, and a vague statement such as the above gives no real assistance toward the proper understanding of the disease. We have, then, to consider this: Is acute rheumatism the result of an infection with various pus-forming micrococci in an attenuated state, or is it the result of an infection with one microörganism only?

The first view, that acute rheumatism is an attenuated pyæmia, is one very widely held. Yet at the present time, in the writer's opinion, those who hold it have never established their position, and to it there are obvious and grave objections. In the first place acute rheumatism is a very common disease—far more common than the various forms of pyæmia; yet it is most exceptional to find that it arises in connection with pyæmia. Now and again there are puzzling cases which follow otitis media or a tonsillar abscess which support this view to some extent. Yet for one of these, hundreds of cases of rheumatism arise in such a way and run such a course that they cannot be grouped as examples of attenuated pyæmia, without making a pure assumption without parallel in the entire field of medicine.

Again, acute rheumatism can be most deadly. What more terrible poisoning can be found than a severe attack with hyperpyrexia? This is certainly not an attenuated infection, and it certainly is not pyæmia. Lastly, because various micrococci, including the staphylococcus aureus, have been found in the tissues and isolated from them in acute rheumatism, this does not constitute a proof that they are a cause of the disease; or because various micrococci have produced arthritis and endocarditis in animals, this is no proof that they are therefore the cause of acute rheumatism. Many infections in man will cause arthritis or endocarditis and yet the conditions need not be acute rheumatism. The cardinal rules of investigation must be adhered to in the study of the etiology of rheumatism; that is to say, a microörganism must be found with constancy in the important lesions of the disease; it must be isolated and cultivated outside the body; it must produce similar lesions in susceptible animals and must be again isolated from these lesions. No proof short of this suffices; and until this proof has been obtained for more than one micrococcus the view that various attenuated micrococci are causes of acute rheumatism is not established.

The second view maintains that the cause is a diplococcus belonging to the group of streptococci allied to the *Streptococcus pyogenes* on the one hand, and to the *Pneumococcus lanceolatus* on the other. This diplococcus has been isolated by a considerable number of investigators and its relationship to the disease worked out step by step within the last ten years. Among the pioneers may be mentioned, Mantle, Klebs, Leyden, Chvostek, Singer, Popoff, Loeffler, and Michaelis. Triboulet and Apert in 1898 placed the position of this diplococcus upon a firmer basis by producing mitral disease in a rabbit from an injection of the microörganism obtained from the blood of a patient with rheumatic fever.

Westphal, Wassermann, and Malkoff, in 1899, produced fever and multiple arthritis in eighty rabbits with a similar microörganism, obtained from a fatal case of rheumatism. Paine and the writer in 1900 published an independent investigation in which they had isolated this diplococcus from 8 successive cases of acute rheumatism and had shown its presence in the most important human lesions; they had produced these various lesions in rabbits and had isolated the diplococcus from the animal tissues. Since that date they have increased the number of cases from 8 to 35, with only occasional failures.

The results of experiment are on the whole remarkably constant, and the reader cannot lose sight of the fact that a microörganism which is present in the lesions of acute rheumatism is capable of reproducing similar lesions in animals. Vernon-Shaw in 1903 demonstrated that monkeys were susceptible to the infection with a culture obtained by the writer from rheumatic pericarditis immediately after death. Fritz Meyer, Ainley Walker and Beatson, Beattie in Edinburgh, Longcope in America, have confirmed many of the observations and have added more facts.

The chief characteristics of the microörganism are: It is a small micrococcus 0.5μ in diameter, and usually grows in pairs or in short chains. As a rule it does not show a capsule, but there is reason to believe that in the human tissues the appearance of capsulation may be occasionally found. It stains readily with aniline dyes. Some writers have stated that it retains Gram's stain; this is undoubtedly correct; but it does not retain this stain with great tenacity.

Degenerative forms are common, and the micrococcus then becomes swollen or pear-shaped. Some discussion has arisen over the name that should be given to it, but there seems no good reason for altering the name that Paine and the writer originally gave to it in 1901—the "Diplococcus rheumaticus," for it will be found in the majority of instances as a diplococcus rather than a streptococcus, and it is a cause of rheumatic fever. If a descriptive name is needed the "Diplococcus rheumaticus" is the most accurate—if a family name is required then "Streptococcus rheumaticus."

Cultural Characteristics.—*In bouillon* at 37° C. there is in twenty-four hours turbidity with slight flocculent deposit. In three days the fluid becomes clear and there is a distinct deposit. The medium becomes acid. *Gelatine (Stab)*—In forty-eight hours minute colonies appear along the track of the needle; there is no liquefaction. *Blood agar*—This medium is one of the most favorable. Fresh blood is smeared upon the agar, and incubated for twenty-four hours. In twenty-four hours after inoculation minute white colonies are visible; these tend to remain discrete, and alter the blood pigment to a rusty brown color. A noteworthy point is the remarkable vitality of the

microörganism upon this medium, and it is interesting to record that the original culture isolated by Paine in 1899 is still growing in subculture. *Milk and bouillon* (equal parts) slightly acidified with lactic acid. This medium is a most serviceable one for isolation of the microörganism. In twenty-four hours the milk is coagulated. *Litmus milk* (blue) is turned a pinkish tint in forty-eight hours and the milk coagulated. Vernon-Shaw found that the best medium was glycerine, veal broth containing 2 per cent. peptone, and 1 per cent. alkaline to phenolphthalein. Beattie[1] finds a definite and very distinctive reaction in the production of acid and precipitation of the bile salts in McConkey's bile salt lactose broth.

A feature of this microörganism is the power it possesses of producing acid. Although a production of acid is a property common to many bacteria, this one possesses the power in a marked degree. Triboulet and Coyon, Walker and Ryffel, Shaw and Berger, have investigated these acids, and it is clear from their investigations that they vary with the medium in which the microorganism is grown. Walker and Ryffel have directed attention to the large quantity of formic acid that the microörganism forms, and have extracted it from the bodies of the microörganisms themselves. Further investigations can alone show how much specific value we can attach to this formation of formic acid. In any case, however, it is a very interesting point that an acid which produces such an irritant effect upon the tissues should be formed in considerable quantity.

Although it is sometimes a difficult matter to demonstrate them, the diplococci are probably present in all the chief rheumatic lesions. At one time or another they have been demonstrated in the endocardial and pericardial tissues, in the pleuræ, peritoneum, pia mater, synovial membranes, nodules, lungs, urine, and blood.

In this article as elsewhere the writer has purposely avoided the use of the term "specific" as applied to the "diplococcus rheumaticus"; and the present position of the etiology appears to him to be this: Acute rheumatism is a *specific disease*, and so far as our knowledge goes owns but one exciting cause, variously called a diplococcus, streptococcus, or micrococcus. The bacteriologist would wish, perhaps, to go further and say that this diplococcus is specific; such may prove to be the case, and is probable; but the discovery of a specific test for a microörganism is a different matter to establishing it as the cause of a specific disease.

The fourth and last view, which maintains that the exciting cause of rheumatism has yet to be demonstrated, rests upon the interpretation put upon experimental investigations with various streptococci derived from sources that were not rheumatic, and upon the fact that the micrococcus of rheumatism is very rarely found in the acute synovial exudations and blood of man. Many investigators, and notably, of late, Cole in Baltimore, have shown that various streptococci may produce an endocarditis and arthritis in rabbits indistinguishable from that produced by the microörganism of rheumatism. They argue from these results that this micrococcus is not in any way specific, and very possibly has no causal part in acute rheumatism.

To the writer, who has also studied the results of various streptococci, such an interpretation has these objections: It is not admissible to omit the first two of the cardinal laws of investigation, and to use experimental results

[1] *British Medical Journal*, December 22, 1906.

with micrococci which have not been obtained from cases of acute rheumatism, as evidence for or against the cause of the disease. Such a procedure involves the assumption that lesions which have a superficial resemblance to one another are identical and is a very dangerous one. In man, for example, early endocarditis, whether pneumococcal, rheumatic, staphylococcal, or tuberculous in causation, has much the same superficial appearance; yet the diseases are widely different. It is difficult, moreover, to explain away the fact that a microörganism which has been repeatedly *isolated from the lesions of rheumatic fever* should produce with remarkable constancy the lesions of that disease in animals, and that these lesions should occur not only in rabbits but also in monkeys.[1]

This view would perhaps have had more weight if rheumatism in man were the only cause of endocarditis and arthritis; but it is well known that many allied but not identical diseases produce these effects in man as well as animals. Little value, again, can be attached to the negative results that have been obtained from investigations of the blood and synovial exudations in acute rheumatism.

It may be asked, How often would early local tuberculosis be detected from examinations of the blood, or of a small quantity of fluid from a tuberculous pleurisy? Yet the tubercle bacillus is far easier to demonstrate than the minute diplococcus of rheumatism.

Predisposing Causes.—There is much to be learned about these and it is possible that the acceptance of the view that the disease is infective in origin will in the future clear up some of the obscurity.

Heredity is admitted as a very important predisposing cause, and in studying a long series of cases one cannot but be struck by the great frequency with which a family history of the disease is obtained after all allowance has been made for the vague use of the word "rheumatism." This hereditary tendency is especially marked when it is transmitted from both sides of the family, and it shows itself by a special vulnerability. A distinction should be drawn between the rheumatic diathesis and those rare cases in which the mother has suffered from acute rheumatism during pregnancy and the child is born with active carditis. In these cases there is probably a direct infection through the placental circulation.

Age.—Acute rheumatism is rare under five years of age, but from that time up to fifteen its frequency greatly increases; throughout adult life it is met with, but in advancing years the tendency diminishes considerably. It is an error to suppose that this disease occurs more frequently in adult life than in childhood.

Sex.—Except in so far that the male adult is more exposed to sudden chills and severe exposure by virtue of his occupation, there is no striking difference.

Climate, Season, and Locality.—Acute rheumatism, as Hirsch pointed out, is ubiquitous, but is more frequent and severe in temperate and changeable climates. The majority of cases occur in autumn and spring; the fewest occur in summer; but they are met with all the year around. It is essentially an urban disease, favored by cold winds and damp. Newsholme associates it with a low level of ground water; in London, certainly, acute rheumatism

[1]Some bacteriologists have suggested that the diplococcus occurs in a terminal infection. There is a patient living now and in active work from whose blood Paine and the writer isolated the diplococcus seven years ago, during an attack of acute rheumatic pericarditis.

is more rife and more severe when the cold and rain of autumn commence after a hot, dry summer.

Damp alone does not explain the frequency of the acute rheumatism, if—as seems to be the case—it is true that it is an urban disease and more severe when the subsoil water-level is low. A sudden chill when the body is heated, or undue exposure to damp when the body is over-fatigued and the mind overtaxed, are among the most usually cited antecedents. It must be confessed that very often there is no convincing history of chill or damp. In a certain number of cases a very definite history of living in a damp house has been associated with the development of acute rheumatism, but in many more there is no such history to be obtained.

Epidemics.—There is a good deal of evidence to show, as Chomel, Hirsch, Lange, and others, have maintained, that there are waves of acute rheumatism; and, in addition, the character of the disease alters in different outbreaks. Closely allied to epidemic occurrence is the possibility of spread by contagion, and some remarkable examples have been recorded. There are nevertheless difficulties in establishing the truth of this—partly owing to the strong hereditary tendency to the disease, and partly to the probable influence of atmospheric conditions. It is not uncommon to find that two and even three children in a family of rheumatic parentage are simultaneously attacked but this does not prove the contagiousness of acute rheumatism.

Diet.—Diet does not appear to have any marked effect upon the incidence, and it seems improbable that an excess of meat or carbohydrate is a cause. Excess of uric acid has in the writer's opinion no immediate bearing on the causation.

Pathology.—The pathological changes are for the most part easily understood. The exact nature of the changes produced by the toxins cannot, it is true, be demonstrated, but the macroscopic and microscopic appearances are quite explicable. It is important to bear in mind that these lesions, the carditis, arthritis, nodule formation, pleurisy, etc., are primarily due to the local deposition of the bacteria in these situations, and not the result of toxins only. The bacterial infection in acute rheumatism is widespread and not localized as in diphtheria.

From this infection of the various tissues three types of injury result:

1. The simple type.
2. The fibroid type.
3 The malignant type.

1. In the simple type, which is illustrated by acute rheumatic arthritis, the bacteria are rapidly destroyed by the resistance of the tissues, and the resulting inflammation quickly subsides. If the infection is more severe, or the resistance imperfect, death of some part of the affected tissues will occur, and with resolution this dead tissue is replaced by scar formation. The thickening of the mitral valve after acute simple endocarditis illustrates this repair.

The microscopic changes are dilatation and sometimes rupture of the blood capillaries, with well-marked swelling of the connective tissues in their neighborhood. Where the process is most severe the connective tissues pass from the stage of swelling to that of necrosis and the area is invaded with leukocytes. With resolution fibroblasts invade the necrotic area and thus a scar is formed. When these changes occur in the subendothelial tissues of a serous membrane, such as the synovial, pericardial, or pleural, there is a rapid exudation into the serous cavity of a clear or blood-stained fluid which

later becomes sero-fibrinous. It is often said that suppuration does not occur in acute rheumatism, and this is true enough if the term suppuration is restricted to the yellow fluid found in pyæmic abscesses, empyema, etc. In severe rheumatic pericarditis, however, the condition is in the author's opinion to all intents a *rheumatic* suppuration.

The relation of the bacteria to the exudations is interesting and easily understood; yet their absence from the early exudations has more than any other single fact influenced investigators against the bacterial origin of acute rheumatism. These diplococci escaping from the minute blood capillaries are necessarily at first located in the subendothelial tissues, and the endothelium serves as a bar to their escape into the serous cavity. For this reason there is great difficulty in finding them in acute effusions into the joints or other serous cavities. Later, again, when after a severe infection their poisons have destroyed the protective endothelium and they have escaped into the serous cavities, the leukocytes attack and destroy them. The particular phase in which the bacteria can be easily obtained is the comparatively rare one in which many have escaped into the fluid and the leukocytes have failed or have not had time to destroy them.

2. *The fibroid type* of lesion is best exemplified by the well-known condition of mitral stenosis. For some reason, as yet unexplained, this type is more frequently found in the female sex. It is a subacute inflammation very persistent in character, which without causing any considerable amount of necrosis produces a gradual sclerosis. It is also met with in some cases of persistent subacute pericarditis, and in those cases of rheumatic arthritis in which there is much swelling of the periarticular tissue and which run a protracted course. It may be objected that there is no line of demarcation to be drawn between the simple and fibroid type of inflammation; but there is this practical value in the recognition of them, that it brings into prominence the difference in the prognosis of the lesions, and emphasizes the persistent nature of the rheumatism in the fibroid type of the disease.

3. The malignant type is best exemplified by certain cases of rheumatic endocarditis in which the microörganisms are not destroyed in the tissues but multiply in the damaged valve and are then disseminated by the blood stream throughout the system. In the most severe form the vegetations on the valve are minute, and yet there are immense numbers of bacteria in them; in those of less severity there are large fungating vegetations in which many bacteria may be present, but in which many are destroyed. A further allusion is made to this condition under the cardiac lesions of acute rheumatism.

The intimate changes produced by the rheumatic toxins are not known; but one condition is clearly recognized, namely, fatty degeneration. This is sometimes very well marked in the cardiac muscle and also in the convoluted tubules of the kidneys when they are severely attacked.[1] The changes in the nervous tissues in rheumatic chorea are not as yet thoroughly determined.[2]

[1] Beattie, *British Medical Journal*, November 24, 1906, has found amyloid degeneration in four cases.

[2] Gordon Holmes and the writer, *Lancet*, October 13, 1906, have recently investigated 3 cases of fatal chorea and found—1. The diplococcus in the pia mater and brain. 2. Vascular and inflammatory changes in the central nervous system and its membranes. 3. Changes in the nervous tissue itself, some destructive and secondary to the vascular changes, others due to alteration in the morphological characters of the nerve cells.

The above outline will give the reader a general plan of the morbid changes in acute rheumatism; under the particular organs some more details will be given which will assist in making clearer the explanation of the clinical symptoms.

General Symptoms.—In attempting to give a description of the onset and course of this disease the difficulty of obtaining a satisfactory nomenclature becomes very apparent. Neither the term acute rheumatism nor rheumatic fever is satisfactory, and we clearly need a general term corresponding to tuberculosis. The word "rheumatism" will be used here in this general sense.

Onset.—The onset of rheumatism, especially in childhood, differs widely in its characters. Thus it may be insidious and preceded by a period of indefinite illness, which can be but compared to the gradual failure of health that so frequently precedes acute tuberculosis. The following symptoms are met with, among others, in this prodromal stage: anæmia, nervousness, irritability, epistaxis, loss of energy, wasting, headache, sore throat, epigastric pain, and fleeting pains in the joints. The temperature is usually above the normal, *e. g.*, 99.5° F.

Children of rheumatic stock may complain of these indefinite symptoms for long periods before they are attacked by acute rheumatism, as for example, in the case of a little girl who was under the writer's care for four years and during that time continually showed one or other of these symptoms. Her mother had suffered from rheumatic fever, and it was clear that the child was repeatedly on the verge of acute rheumatism. At last one summer her mother took her to the seaside, where she paddled about on the sands, apparently was chilled, and as a result developed a sore throat. This was followed by chorea and mitral endocarditis; since that time she has had several definite attacks of acute rheumatism. The manifestation which commences in this insidious way is most frequently chorea.

When, on the other hand, the onset is acute, there may be some definite history of chill or exposure from which the illness is dated, and the first symptoms generally show themselves within a week of this. In the child these are generally sore throat, malaise, fever, pains in the limbs, and prostration. The symptoms of the developed disease vary in accordance with the organs chiefly attacked; thus multiple and painful arthritis, as in the adult, may be the prominent symptom, or chorea, precordial pain and dyspnœa. In severe attacks several manifestations may develop within a few days. The following is an illustrative case: B. J., aged four and one-half years, had been ailing for a few days, when in the night he suddenly screamed out with pain in his head. In the morning he complained of headache and showed choreiform movements; from that time he also suffered from pains in all the limbs. Five days later there was severe general chorea and endocarditis, which was rapidly followed by pericarditis and death. In this case the cerebral symptoms first attracted attention.

In some rare cases the subcutaneous nodules have first attracted attention; in others, a rheumatic eruption.

In the adult the disease may commence in the same insidious manner as in the child; but the acute articular disease is more usual, and when fully developed is characteristic. There may be sore throat, chilly feelings, or even a rigor, and, with these, general malaise, muscular pains, and weakness. The articular symptoms sometimes develop with great rapidity. There is profuse

sweating which is but rarely seen in the child, and the sour odor arising from this has long been pointed out as a feature of the disease. If there is excessive sweating a sudaminal rash not infrequently appears on the trunk. The sufferer lies in bed, quite helpless and dreading any movement; many of the larger joints and sometimes the smaller ones are swollen and extremely tender. There may be a red flush over the articulations that are most severely attacked, and the implication of the tendons and periarticular tissues adds greatly to the distress. Another feature is the rapidity with which the inflammation passes from joint to joint, and also the rapidity with which recovery may occur. Neither in children nor adults is there any characteristic fever. The temperature is moderately raised, 100° to 102° F., and often higher in the adult than in the child. In severe cases the temperature may oscillate considerably in the twenty-four hours. A manifestation which is apt to raise the temperature considerably is a patch of bronchopneumonia.

When much fluid is lost through sweating there is considerable thirst, the appetite is poor, and the bowels constipated. The pulse is usually more rapid than normal and the wave large and easily compressible, and both in adults and children dilatation of the heart is common. The mind is clear and as a rule acute; not infrequently there is anxiety, mental distress, and insomnia, from the pain. The respiratory system is not usually damaged. The urine is scanty, high colored, and strongly acid; the chlorides are diminished and the urates increased. Hæmatoporphyrin is sometimes present in considerable quantities.

Course.—There are few diseases which run a more variable course than acute rheumatism. In children it is impossible to give any definite rule, for it will greatly depend upon whether the heart is damaged. Then again in children there repeatedly occur those cases of virulent rheumatism which are never very acute, but which on the other hand never subside; week after week, month after month, one manifestation after another appears, and when death ensues, eighteen months later, for example, it may be truly said that the child was never free from rheumatism after the first onset of the symptoms. How closely this recalls the course of a chronic generalizing tuberculosis in childhood need hardly be insisted upon. Nevertheless there are many cases in which, as in adults, the acute symptoms have entirely disappeared in three weeks. In the adult it is the frequency of the articular type that gives a more uniform character to the disease. Yet even in this type there is the same tendency to recrudescence of the symptoms—or, as they are generally termed, to relapses—which may protract the illness over many weeks.

Recovery is generally slow, and long after it is otherwise complete, the joints may remain stiff and the muscles tender. A fatal termination is fortunately rare; when it occurs the most usual cause is acute heart disease; but the most fatal complication is hyperpyrexia.

In this general description no separation has been made, as is so often done between rheumatism in the adult and rheumatism in childhood; for this separation is apt to give an imperfect idea of the disease, and this more especially because it has been the custom to write of the disease in the adult as if it were the type. Nevertheless there is much practical value in due recognition of the special features of rheumatism in childhood, and these are put in tabular form:

1. The onset is frequently insidious, with a prodromal stage in which lassitude, anæmia, epistaxis, and epigastric pain, etc., occur.

2. The manifestations are more varied, and, in accord with all infective diseases, the system more generally invaded in the child. The most frequent of these manifestations are:

a. Chorea.
b. Articular pains and swelling.
c. Tonsillitis.
d. Carditis.
e. Erythema multiforme.
f. Pleurisy and pneumonia.
g. Subcutaneous nodules.

3. The occurrence of heart disease is more frequent than in the adult, and for this reason acute rheumatism is more fatal in childhood.

4. Articular complications, though frequent, are less severe than in the adult.

5. Sweating is less common.

6. Nervous symptoms are more often met with, notably chorea; but hyperpyrexia is less frequent.

7. There is a greater tendency for the child to drift into the rheumatic state.

8. Subcutaneous nodules are much more common.

9. Malignant rheumatic endocarditis is less common.

10. The anæmia is often more profound.

After this preliminary account of the general symptoms of rheumatism it is necessary to study in more detail the important visceral lesions. Just as the writer upon tuberculosis will treat of general tuberculosis and then describe tuberculosis of each important organ, so must the writer deal with rheumatism in order to present with clearness a picture of its far-reaching effects.

The various manifestations of acute rheumatism are considered under the following headings:

1. Those connected with the cardiovascular system.
2. Those connected with the joints, muscles, tendons, and fasciæ.
3. Those connected with the nervous system.
4. Those connected with the respiratory system.
5. Those connected with the cutaneous system.
6. Rarer manifestations: (i) alimentary, (ii) genito-urinary, (iii) miscellaneous.

These subjects are dealt with only in so far as they form a picture of active rheumatism.

Cardiovascular System.—It is the frequent implication of the heart that makes acute rheumatism one of the most formidable diseases in temperate climates; and the study of the heart affections is one of much practical importance. Experimental evidence has shown that a diplococcus which is present in human cardiac tissues damaged by acute rheumatism, can produce endocarditis, pericarditis, and fatty degeneration of the myocardium with dilatation of the heart both in rabbits and monkeys. These animals may sometimes recover from this acute endocarditis and a healing lesion be found if they are killed later.

The chief cardiac lesions in man are: (1) acute dilatation of the heart, (2) endocarditis, and (3) pericarditis. In almost all the severe cases, however, the damage is a complex one; that is to say, the endocardium, myocardium, and pericardium, are affected, and to this condition the term "carditis" is often applied.

There are very considerable differences in the development of these lesions. Sometimes the attack is rapid and severe, and in a short time the heart is terribly injured; in others there is an insidious onset and a gradual downhill progress; while in yet others the damage is as fleeting as that to the joints. It is accordingly most essential to recognize the earliest warning of heart disease, in order that the patient may be at once placed under strict treatment. This warning is, as a rule, acute dilatation of the heart, the importance of which has long been insisted on by D. B. Lees. The evidences of it are the following: (1) A slight rise in the frequency of the pulse rate. (2) The cardiac impulse becomes diffuse and extends beyond the vertical nipple line. (3) The area of deep or relative cardiac dulness is increased to the left, and sometimes to the right and upward. (4) The first sound at the apex becomes short, and the second sound in the pulmonary area is accentuated. (5) A soft systolic murmur cannot infrequently be detected internal to the left vertical nipple line. These are the earliest clinical signs of rheumatic heart disease, and this condition of dilatation may entirely disappear.

The rapidity with which dilatation may occur in the course of acute rheumatism is most remarkable, and this is true both of the adult and the child. The explanation, however, is not easy unless it be associated with some sudden damage to the cardiac nerves. The patient shows but few signs of cardiac dilatation unless it is acute and severe. If he has not been confined to bed there is shortness of breath on exertion, with a sensation of faintness and weakness. When more severe there are muscular weakness, pallor, restlessness, and well-marked dyspnœa.

Allusion has already been made to the production of myocardial disease in animals by experimental inoculations of the diplococcus; fatty changes in the cardiac muscle fibers are thus produced, together with dilatation and antemortem thrombosis. These facts are both interesting and important, for there are exceptional instances on record in which death has also occurred in man from acute rheumatic dilatation of the heart, and these experiments afford strong support to the reality of dilatation of the heart in acute rheumatism. In these rare and fatal cases of acute dilatation the symptoms are most urgent. They are dyspnœa, pallor, vomiting, and delirium; the pulse is rapid and feeble, and the heart irregular, with no palpable impulse. The sounds become almost inaudible, although a mitral murmur may be heard in the region of the left nipple. The end may be by sudden syncope. In passing, the writer would also emphasize a definite group of cases in which the dilatation of the heart remains more or less chronic and relapsing. These are intractable in their course, and the patients suffer much from an irritable action of the heart, from breathlessness and nervousness. A superficial observer may miss the dilatation, and, hearing no murmur, dismiss such a case as functional. In so doing a grave error is committed. They recall a condition met with after influenza and some cases of diphtheria.

Endocarditis.—Endocarditis is of more frequent occurrence than pericarditis, and is an exceedingly important event in the history of acute rheumatism. The valves on the left side suffer more than those on the right, although in childhood the tricuspid valve is not infrequently damaged to a small degree. The tendency for endocarditis to attack the left side is also seen in experimental endocarditis, and experiment further shows that the infection is by way of the coronary arteries. This tells against the view

that the special involvement of the left side of the heart in acute rheumatism is due to the presence there of arterial blood. A single valve or more than one may be damaged, and in childhood multiple valvular lesions are common.

Acute simple endocarditis gives rise to but few symptoms, and it frequently happens that a patient comes under observation with a valvular lesion of which he can give no clear history. On this account there are few more important rules in medicine than "in all cases of suspected rheumatism to examine the heart repeatedly." A rise in temperature of a degree or more, accompanied with pain in the chest, palpitation, and breathlessness, are suggestive, and examination of the heart may show that the action is unduly rapid, and that there is some dilatation; a bruit may be audible in an area dependent upon the particular valve that is attacked.

(*a*) *Mitral Endocarditis.*—The first result of this lesion is regurgitation, which shows itself by a soft systolic murmur audible at the apex and traceable toward the axilla. In some cases there is a prolongation of the first sound before the bruit appears, and another important physical sign is a persistent reduplication of the second sound at the apex, which points to a thickening of the mitral segments. Lastly, it is not unusual to hear in the child a to and fro murmur over the apex, which is of mitral and not aortic significance.

(*b*) *Aortic Endocarditis.*—The first result of this is aortic regurgitation. Experimental inoculations have caused aortic and mitral endocarditis in animals, and also aortic endocarditis without any other valvular lesion. In man, also, aortic endocarditis may occur as a solitary lesion, although it is more usually combined with the mitral lesion, both resulting from rheumatic inflammation. The physical signs which direct attention to aortic disease in the course of acute rheumatism are the following: (1) Cardiac excitement; (2) a loss of definition of the aortic second sound, and (3) the appearance of a soft diastolic and sometimes also a transient systolic murmur. In children it should be remembered that the aortic diastolic murmur is frequently heard more distinctly to the left of the sternum.

The combined aortic and mitral lesion is a very serious and not very rare occurrence in childhood, and in severe cardiac rheumatism the possibility of this double lesion must always be remembered. It is more common in the male than in the female. Acute endocarditis, if it is severe, soon leaves its impress upon the features of the patient, and this is particularly the case with the aortic lesion in childhood. The anæmia in these cases is well marked, and the striking pallor and forcibly pulsating arteries tell their own tale.

On the other hand although a slight mitral lesion cannot be detected from the aspect of the patient, when it is more severe there is soon noticed a congestion of the bloodvessels of the lips and cheek, which with the purplish tinge of the blood suggests the lesion before the heart is examined. In acute endocarditis œdema, if present, is slight; but in children the face is sometimes puffy, and an appearance results indistinguishable from that of renal disease.

The subacute type of inflammation, which leads to much fibrosis and contraction, is well illustrated by mitral stenosis. This form of rheumatism is more frequent in the female than in the male. So insidious is the onset of this that it may not attract attention. Nevertheless, a careful study of rheumatism in early life proves that it is associated with continued sub-

acute rheumatism. In those prolonged cases of chorea, for example, which drag on for months, and which frequently relapse, this stealthy process can often be traced, surely and slowly crippling the heart.

It would be out of place here to dwell with any detail upon the symptoms of mitral stenosis, for it is a chronic affection; but it will be advisable to touch upon some of the early indications which fall into three classes.

1. There may be the signs of a slight mitral regurgitation, which disappear, to be followed by a progressive abruptness of the first sound. Later this abrupt first sound is noticed in association with a rumbling murmur which is diastolic, mid-diastolic, or presystolic in time, an accentuated pulmonary second sound, and a presystolic thrill.

2. Without any signs of mitral regurgitation, a progressive stenosis, as described above, may develop.

3. Most commonly the signs of stenosis develop in the presence of a persisting mitral regurgitation.

The malignant type of rheumatic inflammation is, in the writer's opinion, illustrated by some cases of malignant endocarditis in patients who have suffered from rheumatic fever. General opinion holds that malignant endocarditis is essentially a different disease to rheumatism; but the evidence in favor of the view that *some* of these cases are rheumatic is very strong. In the first place all members of the micrococcal group to which the diplococcus belongs are capable of producing malignant endocarditis, and it is highly probable that this diplococcus, which so often attacks the heart, would also produce the same condition. Again, if the clinical histories of cases of malignant endocarditis are investigated the most frequent antecedent is found to be acute rheumatism. Some cases, moreover, commence with an onset indistinguishable from acute rheumatism, and exhibit during their course manifestations of the disease; the likeness, in fact, may be so close that even to the end of life it may remain doubtful whether it is simple or malignant endocarditis from which the patient is suffering. The late Dr. Andrewes, Osler, and others, have long pointed out that malignant endocarditis may directly follow acute rheumatism.

These are in themselves suggestive facts, although the view that a secondary infection has been grafted upon the rheumatic one can still be maintained for their explanation. When, however, we turn to accurate experiment there is much more definite evidence. Paine and the writer showed in 1902 that, in some of these cases of malignant endocarditis, with a rheumatic history, the diplococcus can be obtained in pure culture, and can further produce in rabbits not only simple and malignant endocarditis, but every stage between them. Again, with the diplococcus isolated from simple endocarditis of rheumatic origin, it is possible to produce not only the multiple lesions of acute rheumatism but also malignant endocarditis. Lastly, a first inoculation may produce simple endocarditis and another six months later produce the malignant type in the same animal. Further, these experiments teach that the test of the malignancy of a case of endocarditis is not the fungation of the vegetations, but the activity

FIG. 68.

Malignant endocarditis of the mitral valve; produced by intravenous injection of the diplococcus rheumaticus into a rabbit.

of the diplococci in the valve. The vegetations may be minute but the malignancy great, and the vegetations may be exuberant and yet the case be subacute. Although often called arterial pyæmia, suppuration in these forms of malignant endocarditis is rare both in men and animals, although white infarcts are commonly discovered in both. The virulence of the infection sufficiently explains the "septic" type of these cases. This condition is fortunately a rare one and doubtless requires secondary causes to aid in its production. Among such causes are: previous damage of the valves by former attacks of acute rheumatism, constitutions debilitated by unhealthy surroundings, the puerperal state, and probably anæmia.

The malignant type of endocarditis is to be suspected when there is a persistent and irregular fever and the appearance of the patient suggests severe poisoning. In a considerable number of cases there is a history of previous attacks of cardiac rheumatism, and in some rigors occur, which may be repeated and yet no abscess formation result. One striking feature in the heart is the persistent excitement. The cardiac murmurs may be unusually loud, or vary in character. Anæmia, sweating, diarrhœa, infarction, and purpura, are also important symptoms of this type. Some of these cases run a very protracted course, extending over months; others prove rapidly fatal.

The malignant type is rare in childhood. There is below a brief description of one such case which illustrates the points already emphasized: A. B., a boy aged ten years, had for six weeks before he came under observation suffered from precordial pain and attacks of diarrhœa. Upon examination severe endocarditis of both the aortic and mitral valves was discovered. A year previously he had suffered from rheumatic fever, as had also one of his brothers. When he first came under observation he was anæmic, and there was irregular fever. Three days later pericarditis developed, from which a slow recovery took place. A month later multiple arthritis appeared, and the attacks of diarrhœa, vomiting, and irregular fever continued. The arthritis also disappeared, as had the pericarditis, and then, during the next month, signs of infarction showed in the kidneys and spleen; and at length, after three months of irregular fever, the boy died. The necropsy showed a generally adherent pericardium; the adhesions were subrecent. There was malignant endocarditis of the aortic and mitral valves and white infarcts in the kidneys and spleen. No focus of suppuration was found. The diplococcus was isolated from the valves in pure culture and six rabbits were inoculated intravenously. In three malignant endocarditis resulted, in one pericarditis, and in two dilatation of the heart with fatty degeneration and antemortem thrombosis.

It will be evident in this case that there was no reason for assuming some additional septic infection, and the interpretation seemed inevitable that the rheumatic infection itself had displayed an unusually severe local virulence.

Pericarditis.—The most serious form of heart disease in rheumatism next to malignant endocarditis is pericarditis; yet this is not so much on account of its intrinsic harmfulness as on account of the severe type of infection which accompanies it, and the involvement of the myocardium. It is more frequent in childhood than in adult life. The most characteristic examples develop within the first week of the acute rheumatic attack; but there is no period during the illness in which it may not appear. There are three chief types:

1. Simple acute pericarditis.
2. Chronic relapsing, adhesive pericarditis.
3. Malignant pericarditis.

1. The early symptoms of acute pericarditis are a rise of temperature, precordial pain and dyspnœa. The pulse is excited and the tension low. Pericardial friction is usually detected within twenty-four hours, at the base of the heart, and may rapidly become audible over the entire cardiac area. A more unusual symptom is delirium. The distress in the adult is great, and shows itself in the anxious face and orthopnœa; on the other hand, some children show curiously little discomfort. The great enlargement of precordial dulness, so frequent in pericarditis, is chiefly the result of dilatation of the heart, and not of a large effusion. Ill-omened symptoms are vomiting, restlessness, delirium, and lividity, coupled with progressive signs of cardiac failure. A first attack of pericarditis is not as a rule fatal, but this manifestation is the most frequent cause of death in acute rheumatism.

2. The chronic adhesive type is frequently met with in childhood. This form is subacute, but very intractable, and gives rise to complete and dense pericardial adhesions. It may be associated with mediastinitis, pleuritis, and sometimes also peritonitis; and it is probable that some of those remarkable cases named by American writers—who have contributed much to our knowledge of them—multiple serositis, are the result of rheumatism of this type.

3. The malignant type is rare and best illustrated by the following account of a fatal case: C. D., aged seven years, had an attack of rheumatic fever when six and one-half years of age, from which he had recovered. Three weeks before he came under observation he was attacked by pains in the elbows, shoulders, wrists, and fingers, followed a few days later by precordial pain and dyspnœa. His condition from the first was serious. There was advanced mitral disease, he was pale and thin, and there were numerous rheumatic nodules. His illness extended over three months, and throughout there was irregular fever, each day the temperature rising to 102° to 104° F., and until the last week it never reached the normal. Throughout this time the heart was persistently excited, and the idea of pericarditis was repeatedly suggested, but no definite friction rub could be detected. Crops of nodules came out and the boy gradually sank and died. The necropsy showed a pericardium greatly thickened and generally adherent, partly with subrecent adhesions and partly with recent plastic exudation. The left pleura showed a recent pleurisy. The mitral valve showed thickening and a few recent vegetations, as did also the tricuspid; the other valves were normal.

In this case, as was shown by the extensive pericarditis and the great thickening of the pericardium, there had been a persistent and progressive pericarditis extending over probably the entire three months.

The Blood.—This is much impoverished by acute rheumatism, and extreme even fatal anæmia may result. During the acute phase there is a rapid fall in the number of the red corpuscles, and this anæmia may be very obstinate. A moderate leukocytosis is frequent, and there is in exceptional cases a very marked increase. It is difficult and exceptional to succeed in demonstrating the diplococci in the blood, for they are localized in the various lesions. This can, however, be done when the disease is very severe and generalized, and they can be also occasionally detected in the poly-

morphonuclear leukocytes. Lastly in profound rheumatic poisoning there may be great hæmolysis.

The Arteries, Capillaries, and Veins.—Legroux has recorded acute arteritis, the inflammatory changes commencing in the intima immediately beneath the lining endothelium. Barre has also recently described an acute arteritis of the trachial artery attributed to acute rheumatism. In the subacute lesions, which last over a considerable period of time, a perivascular fibrosis occurs which must, by contracting the lumens of the minute arterioles and capillaries, interfere with the circulation of the affected part—synovial membrane, pericardium, etc.—and thus assist in contributing to the indolent nature of the lesions. It is an interesting speculation whether this process may not, when on an extensive scale, be a factor in arteriocapillary fibrosis.[1]

Phlebitis with venous thrombosis may be a result of the rheumatic infection. In 7 cases under the writer's observation this took place in the large tributaries of the superior vena cava. This complication is to be suspected when a localized œdema of a limb, or of the chest or face, appears somewhat suddenly. If with this there is tenderness along the course of the veins, dilatation of collateral vessels, and lastly the sensation of a thick cord in the position of the vessels, the diagnosis becomes assured. French observers, however, have stated that its occurrence is more frequent in the lower extremities.

Articular, Fascial and Muscular Rheumatism.—Arthritis is the most striking evidence of acute rheumatism. It is a symptom which in adult life comes into such prominence that it has been looked upon as a disease in itself, and termed acute articular rheumatism. The objection to this has been already explained. There is, also, another term in use which must be mentioned here. In many writings there are found such expressions as acute tuberculous rheumatism, gonorrhœal rheumatism, syphilitic rheumatism, and by these are implied an arthritis which is acute, transient, and non-suppurative. This is a most confusing use of the term rheumatism and one that is better abandoned. Every purpose is served by naming the above conditions acute tuberculous arthritis, acute gonorrhœal arthritis, or acute syphilitic arthritis, and the assumptions are avoided that they have any connection with rheumatism, or that rheumatism is necessarily a transient arthritis.

Rheumatic arthritis is generally polyarticular and the larger joints, knees, ankles, shoulders, and hip, are those most frequently attacked. It may, however, be monarticular. No distinction, however, can be drawn between arthritis deformans and rheumatic arthritis from the frequency with which the larger joints are attacked, for in childhood the small articulations of the hand and fingers are often the seat of rheumatic inflammation and the hands may closely resemble the appearance presented by the acute form of arthritis deformans. In some cases in childhood the great-toe joints may resemble those of a gouty man. The acute course of the inflammation and the implication of the tendons surrounding the joints render the arthritis extremely painful. There may be much or little exudation, or there may be great pain with no very definite signs of arthritis at all. The articulations are hot and tender, and there is often a red flush over them or over the surrounding tendons.

[1] Recently in a rabbit by intravenous inoculation, Paine and the writer have produced aortitis with calcification of the first part of the aorta. The lesion occurred in three weeks and there was also multiple arthritis.

In animals arthritis is easily produced by intravenous inoculation of the diplococcus, and in them, too, the neighboring tendons are involved. Further, the stages of the process in animals can be studied in all its phases. There is at first a deposition of the micrococci in the subendothelial connective tissue of the synovial membrane, and, with this, much capillary dilatation, even capillary hemorrhage. The endothelium is phagocytic, and numerous leukocytes pass into the subendothelial connective tissue, and by these means the micrococci are destroyed. The exudation, at first clear or blood stained, later becomes fibrinous, and if the arthritis is very severe much of the endothelium is destroyed and many leukocytes and endothelial cells, together with diplococci, pass into the synovial cavity. The capsular tissues also swell and become gelatinous in appearance, and experiment teaches that this implication of the periarticular tissues adds greatly to the duration of the arthritis and explains the stiffened and painful joints which are so often met with in man.[1]

It is because rheumatic arthritis is often a simple synovitis, and probably because the diplococci are rapidly destroyed in the tissues, that it usually runs such a rapid course. This is a principle not only true for rheumatism but for every infective arthritis. Most experienced physicians have, for example, met with a transient arthritis in pyæmia. This in the writer's opinion should not be explained as a rheumatic arthritis, but as a mild pyæmic infection of the particular joint in which the more destructive processes did not develop because the bacteria were destroyed. The converse is equally true. A rheumatic arthritis may be most obstinate and be followed by grave changes in the bones and cartilages of the joints; yet this is no good reason for calling it non-rheumatic. Though it is unusual for pyæmia to cause a simple synovitis or for rheumatism to cause a destructive arthritis, both are occasional events. A condition of osteo-arthritis and also a chronic synovitis can be produced by the "diplococcus rheumaticus" in rabbits.

In man it is not rare to find one joint in articular rheumatism remain obstinate and painful, and in those cases there will be found considerable periarticular swelling, and the joint may remain permanently crippled. Thus the three types of rheumatic inflammation are illustrated by the usual transient metastatic arthritis, the less common chronic relapsing periarticular type, and the least common acute severe arthritis in which the joints may be drained by the surgeon and classified as "septic."

It is noteworthy that a local inoculation of the micrococcus into the knee joint in a rabbit, will, as Shaw pointed out, sometimes be a cause of endocarditis.

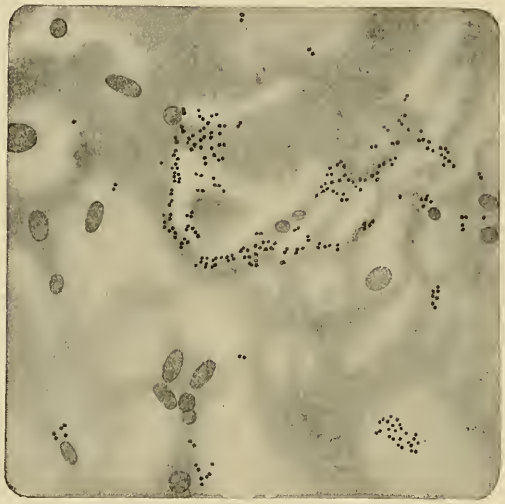
The tendons are often damaged in acute rheumatism by an inflammation of their sheaths; in the acute stage gangliform swellings may appear, and as a sequel painful adhesions sometimes result. *The periosteum* also may be attacked and painful, fixed, periosteal nodes develop. A more chronic process of this nature accounts in some measure for the so-called "growing-out" of bones in rheumatic children.

The most interesting and remarkable of the inflammations in the connective tissues are the *subcutaneous nodules*. These are the result of a

[1]This is certainly not true of the arthritis of acute rheumatic fever as seen in Baltimore. It is exceedingly unusual for any local joint conditions to persist after the attack.—EDITOR.

local deposit of the diplococci in the subcutaneous tissues. The usual changes result; *viz.*, swelling of the connective tissue, dilatation of the blood capillaries, exudation, and necrosis of the most damaged area. The microörganism, as in other rheumatic lesions, is destroyed by the living cells. These nodules are not, as they are so often termed, fibrous nodules, but inflammatory exudations. When, however, the inflammation is chronic, some fibroid change may occur in the necrotic area. Nodules can be produced in rabbits by injection of the diplococcus. In size they vary from a pin's head to an almond, and are often better seen than felt, if the skin

Fig. 69



The diplococcus rheumaticus in a rheumatic nodule.

over them is gently stretched and the light is thrown obliquely. In rare cases the skin over them is reddened and they become adherent to it, and slightly tender; but it is interesting to notice how little discomfort these nodules usually cause, even when they are developing rapidly and in numbers. This manifestation is much more common in childhood and it is one which varies also in frequency with different outbreaks of rheumatism. The nodules should be looked for over the bony prominences and along tendons, as, for example, upon the bony processes around the elbow joint, the edges of the patellæ, along the tendons of the extensors of the fingers and toes, over the parietal and occipital bones, around the ankle joints, over the vertebral spines, along the crests of the ilia, and on the spines of the scapulæ. They may appear and disappear in three days, and cannot for this reason be essentially fibrous.

Their great clinical interest lies in their frequent association with severe cardiac rheumatism. This is not an invariable occurrence, for occasionally they are almost the only rheumatic symptom, but as a general guide the rule (which we owe to Cheadle) that rheumatic nodules are associated with severe heart disease is a valuable one. Their diagnostic value is also considerable, for although nodules are met with in arthritis deformans, gout,

and erythema nodosum, these generally differ in their distribution or appearance. They must as a rule be searched for, although there are exceptional instances in which the parents or patient have made the discovery.

A condition upon which accurate knowledge is more difficult to obtain is that of inflammation of the muscles and their fasciæ. "Muscular rheumatism" may arise from different causes, and to ascertain in how many cases it is truly rheumatic is most difficult. Froriep described in muscular rheumatism the occurrence of localized swellings in the muscles, and recently Stockman has investigated the subject from the standpoint of chronic rheumatism. These swellings are localized connective tissue inflammations which when chronic produce fibrous nodules or strands in the muscular tissue. These nodules or strands may hamper muscular action or press upon nerve fibers. In acute rheumatism A. E. Garrod has noted the occurrence of a node of this kind in a child, and in one case the writer has seen a similar one in the left pectoralis major. The following case is an example in an adult: M. B., aged forty-nine years, was admitted to University College Hospital suffering from acute articular rheumatism. The knees, ankles, elbows, and wrists, were swollen. The temperature was irregular, and varied each day from normal to 101° F. The heart was dilated, but there was no organic valvular lesion. There was continual complaint of pains in the arms and forearms, which she described as feeling as if they were beaten. On careful palpation, six of these nodules could be felt situated deeply in the right deltoid and the extensor longus digitorum. The case was of great severity. It ran a protracted course, but eventually recovery ensued and the nodules slowly disappeared.

It is probable that the stiff neck, pleurodynia, lumbago, and tender feet met with in the rheumatic, are the result of changes of a similar nature.

Manifestations in the Nervous System.—Acute rheumatism is a disease which frequently damages the nervous system, and in its most severe form is often called "cerebral rheumatism." It has been frequently observed that children of rheumatic parentage are often highly nervous and prone to headaches, night terrors, and insomnia—facts which should not be lost sight of by those who have their general management.

Chorea.—There is perhaps no more remarkable condition than chorea, and at the present time no disease promises more hopefully than this to give a clue to the explanation of functional nervous disorders. Its association with rheumatism has been noticed for more than two centuries, and yet the complete explanation of the symptoms remains one of the most difficult problems of the subject, because of the rarity with which opportunities occur for investigating the condition after death. These facts, however, have been ascertained:

1. Chorea is associated very frequently with acute rheumatism.
2. The association is of such a close nature that chorea, when rheumatic, must be looked upon as a manifestation of that disease.
3. The more carefully the examinations of the brain are conducted after death the more frequently are some definite lesions found.
4. Investigators have isolated micrococci from the meninges, cerebrospinal fluid, and brain, in fatal chorea.

In illustration of this last fact allusion must be made to an important case which was published by Westphal, Wassermann and Malkoff, in 1899. These investigators from a fatal case of carditis and chorea in a girl, isolated

a minute diplococcus which produced polyarthritis in a series of 80 rabbits. In 1900, Paine and the writer observed remarkable twitching movements in a rabbit as a result of an intravenous inoculation of a diplococcus obtained from a case of fatal rheumatism. This microörganism was similar to that described by Wassermann. Since that date similar movements in rabbits have been observed by Fritz-Meyer, of Berlin, and Beattie, of Edinburgh; in both cases they were results of inoculations of a similar microörganism. Still more recently Cole has noted involuntary twitching movements from the injection of other streptococci.

It cannot however be pretended that chorea has been reproduced, for in chorea the involvement of the highest nervous centres—the intellectual and emotional—stamps it as a human disease. Nevertheless it is an interesting fact that such movements should have been produced by these inoculations and that the microörganisms have been demonstrated by Paine and the writer in the pia mater and in the blood capillaries passing into the motor cortex of the animal's brain. Since that date, also, they have isolated the diplococcus immediately after death from the cerebrospinal fluid of three further cases of rheumatic chorea, and by cultures from one of them have produced in rabbits not only arthritis, but also endocarditis and pericarditis.[1] The explanation of rheumatic chorea that naturally suggests itself is that the microörganisms gain a foothold in the meninges and brain and probably also in the spinal cord, where, partly by the poisons that are produced and partly by the local lesions, they give rise to the phenomena. Whether, as Triboulet (père) maintained, the peripheral nerves also suffer in chorea, is uncertain. At the present time it seems inadvisable to claim all cases of chorea as rheumatic, for it is but reasonable to suppose that other allied microörganisms may possibly in a lesser degree produce chorea. Upon this point more evidence is needed.

Chorea is far more frequent in childhood[2] than in adult life, and the frequency with which it occurs in the young without any symptoms pointing, on the one hand, to an infection, or, on the other hand, to any excitant cause such as fright, is remarkable. It appears at any period in the course of an attack of rheumatism. The onset is generally insidious, sometimes acute. Among important warnings are night terrors, irritability, worrying over school work, and headache. The last is a remarkably constant symptom. The chief types of chorea are the general, hemiplegic, paralytic, and maniacal. The course varies greatly. An acute case may end abruptly. Slight and insidious cases may drift on for months, and there are some in which the movements last for years. Death from chorea is very rare, but the supervention of pericarditis, or, more rarely, hyperpyrexia, sometimes leads to a fatal termination. In adult life chorea is unusual and the majority of cases occur in women, in whom pregnancy, it is well known, increases the severity of the disease.

[1] Gordon Holmes and the writer, *Lancet*, October 13, 1906, have investigated 3 fatal cases of chorea, including one in pregnancy, and found these changes in the nerve cells: (1) practically all the cortical cells were affected, being swollen and distended; their tigroid had partly disappeared and their nuclei stained more deeply than normal. (2) In some of the cells, the nuclei were shrunken and deformed with the outline of the cell bodies indistinct. There were also small areas of cortical softening.

[2] The writer's youngest patient was aged two years and nine months; she began to show signs of mitral stenosis at three years.

Cerebral Rheumatism (*Gravis*).—The most severe form of cerebral rheumatism is associated with hyperpyrexia, and is, in England, usually termed rheumatic hyperpyrexia. These cases are fortunately rare. The Continental term "cerebral rheumatism," is preferable to that of rheumatic hyperpyrexia, for grave symptoms may arise without extreme fever; and, although the fever is a most important and valuable sign, the general symptoms are not entirely due to it, but are also a result of the profound toxæmia.

The onset occurs as a rule in the third or fourth week of the active disease, although it may also supervene after the temperature has remained normal for more than a fortnight. Unfortunately there are no means of discovering in what cases this particular danger exists, and it may supervene so rapidly that the medical attendent is completely taken by surprise. Warning symptoms are headache, delirium, sleeplessness, and vomiting. In some cases there is cutaneous hyperæsthesia; in others, frequency of micturition. When the condition is more advanced the mental disturbances become more serious, semi-consciousness supervenes, with spasmodic twitchings and irregular breathing; the pupils are contracted and the eyes widely open; the pulse increases in rapidity and the face becomes livid. The temperature may rise gradually and then leap up to 108°, 109°, and 110° F., or it may rise abruptly from the normal to hyperpyrexia. In some cases the other rheumatic symptoms abate when this condition supervenes. Death occurs in over 50 per cent. of the cases which are not promptly treated, and is almost invariable if the temperature rises above 106° F. Many patients die even with prompt treatment. Cerebral rheumatism is not always of this exceedingly severe type, and cases occur in which dangerous symptoms such as delirium, high but not extreme fever, and headache, are met with and then abate, and this may occur more than once in the course of a single attack of rheumatism.

It is exceptional to find any gross cerebral lesion after death, but the subjoined case illustrates the occasional occurrence of meningitis: C. S., a boy aged thirteen years, was admitted on August 26, 1904, into University College Hospital, for arthritis of the ankles and knees, and pains across the chest on drawing breath. The illness had been of four days' duration. The boy's father had suffered from rheumatic fever, but the patient, with the exception of adenoids, had been healthy. His illness was to all appearances a sharp attack of rheumatism. The heart was dilated, and a systolic murmur could be traced from the impulse to the axilla. Both knees were swollen, but there were no other signs of acute rheumatism. The temperature on admission was 103.6° F. On August 28 there was some pain in the left hip joint, but by August 30 all swelling of the joints had disappeared and the temperature had reached normal. Salicylates were continued in small doses, and he did well until September 17. On that day he complained of headache and was sick. In the evening his temperature rose to 102.4°. The next day headache and vomiting continued and the temperature rose to 103.6° F.; on this account he was sponged and seemed better. Early next morning he became unconscious, with widely dilated and fixed pupils. Muscular rigidity was noted on both sides of the body. This was general in distribution and alternated with flaccidity. The temperature in the axilla was 101° F. at 8 P. M. and 102.4° F. at 1 A. M. At 11.30 A. M. the boy was comatose. The temperature in the rectum was 106.4°. All treatment proved unavailing, and he died at 7.40 P.M.

The necropsy showed early endocarditis of the mitral valve in the process of healing; slight and recent pleuropericarditis, and cerebral and spinal meningitis. The meningitis was plastic in type and distributed mainly over the base of the brain. There was no focus of suppuration.

Rheumatic Spinal Lesions.—There is much uncertainty about these lesions, and the question is complicated by the occurrence of arthritis as a result of nervous diseases. This makes it difficult to decide in doubtful cases whether the primary cause is a nervous one and the arthritis a symptom of it, or whether the nervous disorder and the arthritis are both results of some general infection such as acute rheumatism. An interesting example of a probable rheumatic paraplegia is quoted by A. E. Garrod in his monograph on rheumatism. The patient, a case of Alexander Raynault's, was a man aged twenty-four who had passed through repeated attacks of rheumatic fever. His illness commenced with loss of power in the legs and sphincters, and was looked upon as an acute diffuse myelitis. Recovery of power commenced to show itself in two days, and was followed by multiple arthritis, and this in turn by endocarditis and lastly by pneumonia and pleurisy. Other interesting examples are quoted by Garrod. In addition to these more acute conditions of transverse myelitis it would be interesting to study acute anterior poliomyelitis and disseminated sclerosis with a view to discovering whether one of their causes may not be acute rheumatism.

The peripheral nerves also suffer, and there may result either a symmetrical peripheral neuritis or a local neuritis. This may give rise to well-marked sensory symptoms such as tingling, numbness, and partial anæsthesia; or to rapid muscular atrophy and trophic changes. Severe neuralgia, not infrequently affecting the scalp, may also be a result of acute rheumatism, and in some of these cases fugitive swellings apparently œdematous in nature may be detected over the tender points.

In exophthalmic goitre, as Samuel West has pointed out, there is a history of a preceding attack of acute rheumatism more often than would seem likely from the explanation of coincidence; it is nevertheless difficult to trace the association of these two disease. Insanity is an occasional event, which may be in type melancholic, maniacal, or both combined. Whether or not it is a truly rheumatic condition is at present undecided.

Respiratory System.—The occurrence of tonsillitis in acute rheumatism has been remarked upon for many years. Striking examples occur which leave little room for doubt that the throat is one channel of infection. In 1900 Paine and the author isolated from a patient with tonsillitis a diplococcus which resembled in all respects the one they had already isolated from such rheumatic lesions as endocarditis, pericarditis, and arthritis, and it led to similar experimental results. These facts suggested the conclusion, long suspected, that invasion could be through that channel. Fritz-Meyer shortly afterward published some important investigations upon the subject, although these lacked conviction because he had failed to find the microörganism—a diplococcus of similar nature—in other rheumatic manifestations. Recently Frisswell in America has confirmed Meyer's observations. It is clearly most hazardous to draw deductions as to the causation of rheumatism from cultures taken from the throat alone.

The usual appearance of the "sore-throat" in acute rheumatism is a diffuse redness with some swelling of the tonsils and the palatal mucous membrane. Follicular tonsillitis is also met with, and, less commonly, a condition closely

resembling diphtheria, or that found in some cases of scarlet fever. The tonsillitis in acute rheumatism is often but slightly painful, and for that reason easily overlooked. In childhood it may occur as an isolated event in the prolonged history of a rheumatism, and may probably be then interpreted as a successful effort on the part of the tissues to destroy the invading micro-organisms, either entirely at the local site, or to such an extent that those which enter into the system are unable to produce detectable visceral lesions. There is no relation between the severity of the sore throat and the gravity of the attacks of rheumatism.

Lungs and Pleura.—Rheumatic pleurisy is a common occurrence, and can be experimentally produced in animals. It is met with in the majority of cases in which there is severe pericarditis, and adds greatly to the suffering of the patient. It is a serofibrinous inflammation which in the process of resolution is very liable to give rise to adhesions. Adhesions are frequently discovered between the pericardium and the adjacent surfaces of the pleura in fatal pericarditis, and the physical signs of pleurisy in that situation are characteristic. In addition to pain in the chest, there is pleuropericardial friction which must be distinguished from pericardial friction. Pleuropericarditis is a painful complication of pericarditis. Should it occur alone it must not be mistaken for pericarditis itself, for the prognosis is far less grave in pleuropericarditis, where the outer surface only of the parietal pericardium is damaged, than in pericarditis, which is essentially a disease of the heart itself.

Rheumatic pleurisy may and frequently does occur without pericarditis, but how often as a solitary rheumatic manifestation is a disputed point. Nor does one see how an agreement can be come to upon it, since rheumatic pleurisy tends to get well and seldom needs surgical measures. Nevertheless at the present time when the statement is so frequently made that simple pleurisies are tuberculous, this form needs to be taken into account. There is nothing peculiar in the symptoms.

Pneumonia occurs in the severe types of acute rheumatism, and also results in animals from experimental inoculation. It is usually a broncho-pneumonia. The temperature rises rapidly, and an unusually high fever in acute rheumatism, apart from hyperpyrexia, should always suggest the possibility of pneumonia. This is a point of some practical importance, for there is a natural desire not to distress a patient suffering from articular rheumatism by movement, and thus the occurrence of pneumonia may be overlooked. There may be a considerable area of collapse around the pneumonic patch, and this gives the impression of a condition more extensive than that which actually exists. The consolidation may clear up with great rapidity, although the temperature may remain elevated because of other manifestations. Lastly, as in other forms of bronchopneumonia both lungs are liable to simultaneous involvement.

Acute pulmonary œdema is a very rare manifestation. In the three cases observed by the writer, all were complicated with carditis. One recovered; two rapidly died. The necropsies showed an œdema comparable to that in nephritis, involving the upper lobes of the lungs more than the lower. The physical signs are characteristic, for, with great embarrassment of respiration, there appear innumerable fine crepitations. The kidneys do not show gross changes. There is a possibility that very large doses of salicylate of soda may predispose to this highly dangerous condition.

Bronchitis.—The evidence of a rheumatic bronchitis is not certain.

Laryngeal Affections.—Rheumatism of the crico-arytenoid joints, with some laryngitis, have been recorded by Hirsch and other writers.

Cutaneous Manifestations.—The eruption most commonly seen is a form of erythema—an erythema marginatum or an erythema papulatum. Erythema marginatum appears over the trunk and extremities in the form of rings, which are sometimes mistaken for ringworm. The rings are pink, slightly raised, and encircle skin of a livid color. In size they vary considerably, and several may coalesce into large gyrate areas. There are but few symptoms accompanying this eruption, but there may be some local tingling and irritation. As the rash fades it leaves a stain, and if, as is sometimes the case, there have been hemorrhagic areas, these discolored patches last for a long time. In erythema papulatum the papules vary in size, are usually symmetrical, come out in crops (especially upon the dorsal surfaces of the extremities), and fade leaving a stain. In color they are bluish-pink. In both these eruptions there is often a hemorrhagic element. Bullous eruptions are also met with in which the bullæ contain a clear fluid as in pemphigus.

Purpura is also seen during an attack of acute rheumatism. Small macules appear particularly over the lower extremities, and occasionally a curious irregular network is formed by interlacing lines of purpura. Sometimes the purpura is severe and accompanied by sanious bullæ.

A scarlatiniform eruption has also been described. In one case under observation there was a general erythema of the scarlatinal type, but lacking in the punctiform character. There was no reason to believe that it was a case of scarlet fever, and there was no desquamation, although the latter occurrence would not have disproved the rheumatic origin of the rash. Psoriasis appears to be sometimes closely associated with acute rheumatism. In one case a child was suffering from this disease, and as the eruption faded chorea developed. It is nevertheless difficult to trace the exact association of rheumatism and psoriasis, and the same statement applies also to urticaria and scleroderma.

The relationship of erythema nodosum to acute rheumatism is still disputed. At the present time the position stands thus: Erythema nodosum appears to be frequent in the rheumatic, and in some instances to be associated with such active signs of rheumatism as endocarditis and arthritis. On the other hand, many cases of erythema nodosum run a course of their own, and appear to have no relationship with rheumatism, and for these reasons some observers believe it to be a special disease closely allied to, but not identical with, acute rheumatism. Others believe it to be rheumatic, while others again look upon it as symptomatic of various infections and among these the rheumatic. Further investigations are needed to decide these questions. Erythema nodosum appears most frequently upon the shins, in the form of nodes, which vary in size and may become as large as the palm of the hand. The skin is raised and at first pink and exceedingly tender; later the color turns from pink to a bruise-like blue, and the skin may desquamate. This rash may be general although rarely so, and with it there may be subcutaneous nodules over which the skin is not reddened, and which if cut into are proved to be the results of great vascular hyperæmia and serous exudation.

These rheumatic eruptions may be the first symptom of active rheuma-

tism, or may appear during the course of an attack. As with other manifestations the frequency with which cutaneous lesions are noticed differs in different epidemics.

Rarer Manifestations.—*In the Alimentary System.*—It has been frequently noticed that rheumatic children have weak digestion and are liable to bilious attacks and diarrhœa; but it is difficult to assign a part in their causation to active rheumatism, and it is doubtful whether the epigastric pain that rheumatic children so often mention is gastric in origin. Acute dilatation of the stomach may, though rarely, follow acute rheumatism. Peritonitis is a more common occurrence, and in fatal cases of acute rheumatism a chronic peritonitis may be found around the liver and spleen. On one occasion the writer has heard loud peritoneal friction during life; and in another there was complaint of abdominal pain over the upper segment of the abdomen, and peritonitis was demonstrated, after death, in this position. It has also been produced experimentally, and, further, the micrococcus has been isolated from the exudation in man. Some authorities believe acute rheumatism to be a frequent cause of appendicitis; the writer has never seen a conclusive case, nor, on the other hand, found any change in the appendix in fatal rheumatism.

Genito-urinary System.—Among the rarer incidents of acute rheumatism is the occurrence of acute nephritis, and experimental investigation has thrown considerable light upon this subject. The diplococcus is freely excreted in the urine of animals that have been injected intravenously, and can be isolated from the urine of patients suffering from acute rheumatic pericarditis. In rare instances, as observed by Paine and the writer and Vernon Shaw, acute nephritis may also result from these inoculations. The former have observed it in rabbits and in a cat. The cat within three days of inoculation developed profuse hæmaturia from which it eventually made a perfect recovery; during this period the urine swarmed with diplococci. After recovery the animal was killed and no trace of endocarditis was discovered, which is important as it excluded the possibility of a gross infarct.

Acute nephritis has also been recorded in man by various writers, among them George Johnson, Leyden, Dickinson, Hayem, Lees, and Garrod. The author has met with several instances in childhood. Then again there are interesting examples of the occurrence of renal disease in several members of a family in which there is also a marked history of acute rheumatism. Yet another point of interest is the occurrence in man of large white kidneys in some cases of malignant endocarditis, and of nephritis with continuous hæmaturia in others, to which especial attention has been drawn by Litten. A condition of large white kidney has also been produced by experimental inoculation of the diplococcus into rabbits, occurring in conjunction with malignant endocarditis.

A far more difficult question is the possible influence of rheumatism in causing chronic renal disease. Leyden has directed attention to the fact that although acute rheumatic nephritis as a rule clears up rapidly, there are cases in which it drifts into a chronic nephritis. Can rheumatism, in addition to this, produce a change in the kidney, one which is never acute, but which terminates in a granular condition? It must be admitted that very many cases of acute rheumatism show no changes in the urine so far as albumin and blood are concerned; yet, on the other hand, in acute arth-

ritic rheumatism, and even in chorea, albuminuria is not very rare, especially when the patient has not had sufficient rest. This albuminuria rapidly disappears, but may occur again on exertion and resemble in its behavior orthostatic albuminuria.

It is conceivable that in such cases there may be insidious damage to the kidney which slowly increases in a manner comparable to the slow contraction of the valve in mitral stenosis, and Beattie has observed experimental interstitial nephritis. This, too, is not altogether hypothetical, for a granular condition of the kidney is frequently met with in necropsies upon mitral stenosis. The following table of necropsies exemplifies this point:

1. F., aged 48.—Repeated rheumatism—mitral stenosis. Kidneys—passive congestion, scarring, atrophy of cortices, fatty changes in convoluted tubules.
2. F., aged 60.—Rheumatism, mitral stenosis, granular kidneys.
3. M., aged 43.—Adherent pericardium, granular kidneys.
4. F., aged 37.—Mitral and tricuspid stenosis, granular kidneys.
5. F., aged 45.—Adherent pericardium; kidneys much diseased, small, and hard.
6. M., aged 35.—Mitral stenosis, granular kidneys.
7. F., aged 27.—Slight pericarditis, small kidneys, cortices much wasted.
8. F., aged 41.—Mitral stenosis, granular kidneys.
9. F., aged 44.—Adherent pericardium, mitral stenosis, granular kidneys.
10. F., aged 45.—Mitral stenosis, granular kidneys.
11. F., aged 58.—Rheumatism twelve years before; mitral stenosis, granular kidneys.
12. M., aged 51.—Mitral stenosis, granular kidneys.
13. F., aged 42.—Mitral stenosis, granular kidneys.
14. F., aged 20.—Third attack of acute rheumatism; endocarditis, pericarditis, pleuritis. Kidneys—capsules slightly adherent, finely granular; parenchyma degenerated.
15. F., aged 39.—Three attacks of acute rheumatism; mitral stenosis, granular kidneys.
16. M., aged 22.—Acute rheumatism—repeated attacks—recent and old mitral disease; kidneys large, capsules slightly adherent, and cysts.
17. F., aged 45.—Mitral stenosis, granular kidneys.
18. F., aged 19.—Acute rheumatism at 12; mitral disease, albuminuria. Kidneys large and pale, with adherent capsules.
19. M., aged (?).—Three attacks of acute rheumatism; peri-, endo-, and myocarditis; granular kidneys, with adherent capsules and some thickening of the arterioles in the kidney.
20. F., aged 45.—Mitral stenosis, granular kidneys.

This list is open to the obvious criticism that in patients over forty there are many factors tending to cause cirrhosis of the kidneys; nevertheless it is suggestive.

The Influence of Pregnancy and the Puerperium upon Acute Rheumatism.—This has hardly received sufficient attention. As a general rule it may be stated that pregnancy and the puerperal state tend to produce the malignant type. The severity of chorea in pregnancy is well recognized, and there is but little doubt that in a considerable number of such cases there has been a very definite history of acute rheumatism or chorea in earlier life.[1] The same intensification is sometimes noticeable with rheumatic carditis, which may become active and develop into the malignant type and prove rapidly fatal. In connection with this it is of interest that Paine and the writer observed that a rabbit which had recovered from acute rheumatism with endocarditis and arthritis, died rapidly on re-infection, when pregnant,

[1] French and Hicks, *Practitioner*, August, 1906, found in 29 consecutive cases a history of previous rheumatism in 19 and 15 of the 19 had suffered from chorea.

from malignant and aortic endocarditis. The same type of endocarditis was also noted by Shaw under similar circumstances.

Mastitis.—Still has directed the writer's attention to the possibility of a rheumatic mastitis in childhood, and recently two children have been under observation with active rheumatism and mastitis of the left breast. More extensive observations are needed before any conclusions can be drawn upon this point.

Thyroiditis has been observed occasionally; and in chorea, also, there is sometimes complaint of pain in the thyroid gland, and, more rarely, some swelling and tenderness is observed. *Parotitis* has also been recorded.

Lymphadenitis.—In all cases of fatal rheumatic pericarditis the mediastinal glands are considerably enlarged, and in some cases of tonsillitis associated with acute rheumatism the cervical glands are swollen. It is most exceptional—although on record—to meet with a general enlargement of the lymphatic glands.

Eye.—Conjunctivitis, erythematous and phlyctenular, is met with, and in rare cases acute iridocyclitis complicates an acute attack of rheumatism. This latter lesion is occasionally produced in rabbits by the intravenous inoculation of the diplococcus. The relation, if any, to acute rheumatism, of the persistent, painful, relapsing iritis which is occasionally met with in those with an arthritic family history, has not yet been ascertained.

Diagnosis.—The diagnosis of acute rheumatism, if of the articular type and in an adult, is a simple enough matter. The multiple and painful arthritis, the sweating, thickly coated tongue, dilated heart, metastatic character of the articular lesions, and the reaction to salicylate of sodium, with rapid subsidence of the arthritis, all combine to make the disease a very characteristic one. It is, however, a very different matter when the disease is abarticular, the onset gradual, or the symptoms unusual; and although this division is in no sense a scientific one it will serve to make this part of the subject clearer if the diagnosis is first considered in the child and then in the adult.

1. **In Childhood.**—In many cases, if this is not a contradiction in terms, children with a rheumatic family history drift *gradually* into acute rheumatism. They are "out of sorts" for some weeks, with malaise, wasting, nervousness, slight fever, and fleeting pains. Such an occurrence in children of this type should suggest the possibility of an acute attack in the near future. Fever, multiple arthritis, and cardiac dilatation, in a child usually mean rheumatic fever. When, however, the arthritis is absent but the pains in and around the joints are severe, there is a considerable liability to error.

One serious mistake is to confuse *acute osteomyelitis* and acute rheumatism, for a life may be lost by procrastination. From the first acute osteomyelitis is a serious condition. There may be shivering or actual rigors, the pain in the affected limb or limbs is very severe, and the region of the inflammation rapidly becomes swollen and sometimes brawny. Importance must be attached to the position of greatest tenderness—which is over the epiphysis and not in the joint—to the high fever, prostration, and delirium. The best safeguard against error is the knowledge of its possibility.

A more difficult problem is sometimes offered by *acute anterior poliomyelitis*, for in the early phase of this disease there is often a good deal of pain and fever. A loss of reflex, if it occurs, is a valuable aid, as also marked

wasting. It is in the early stage that there may be great doubt and an opinion may need to be given with caution. There is no swelling of the joints nor heart disease in anterior poliomyelitis unless, as seems possible, some cases are a manifestation of rheumatism in infancy.

A mistake that is made more often perhaps than would be expected is that of confusing *infantile scurvy* with acute rheumatism. Scurvy is not uncommon under two years of age, but rheumatic fever is exceedingly rare. In a doubtful case at this age scurvy should always come first into the mind of the practitioner. The gums must be examined for ecchymoses, the bones for periosteal swellings, and the skin for purpura. Hemorrhages from the kidneys or from mucous surfaces, pallor of the face, and extreme tenderness, are suggestive of scurvy. The heart is not damaged, and, when once this condition is remembered, the diet and the result of its alteration will soon solve any doubt. This mistake also is a serious one, and very damaging to the reputation of the physician; for scurvy is a disease which is most amenable to treatment.

Congenital Syphilis.—There are two conditions in congenital syphilis which may give rise to confusion. The first is the comparatively uncommon pseudoparalysis. In some instances this is accompanied by epiphyseal swellings; in others no swelling can be detected. Here again it is the pain which gives rise to the error. An inquiry into the history, the complexion of the child, its age, and the presence of the well-known stigmata of congenital syphilis, will prevent this error. The fact that the swelling is epiphyseal and not articular is also important. The second condition is met with in older children, and is a syphilitic arthritis. There are different forms of this, and although many joints may be damaged the knees are the most frequently attacked. The course is slow and the condition not very painful. It is a lesion which is associated with interstitial keratitis, peg teeth, and syphilitic deafness. The heart is usually spared, and there is no history of a previous attack of rheumatic fever. In some cases mercurial treatment is most successful, yet this is not the case in all.

Gonococcal arthritis, if due to infection from the mother, shows itself in the first five weeks of life, and is usually associated with ophthalmia. It is uninfluenced by treatment with salicylates.

It may seem almost fanciful to mention *appendicitis* as a possible cause of confusion, yet in childhood this difficulty may arise. The particular cases are those in which acute rheumatism affects only one joint, and that the right hip. In such cases children are apt to refer the pain above Poupart's ligament over the region of the appendix. It is especially important at the present time, when early operations are so frequent in appendicitis, that this error should be avoided. These cases are unusual, and as a rule other joints are soon affected or other manifestations of rheumatism develop.

Acute Tuberculous Arthritis.—The writings of Poncet, of Lyons, in the last few years have brought into prominence a condition of acute and multiple arthritis due to tuberculous infection. Clinically, this arthritis is indistinguishable from the rheumatic, but proof has been furnished in a certain number of cases by the demonstration of tubercle bacilli in the joints. As a rule the differential diagnosis turns upon the presence of active tuberculosis elsewhere and the absence of any history of rheumatic fever.

There is a curious group of cases of multiple arthritis which has been carefully described by Still. The cause is unknown, although in some cases tuberculosis has been claimed as one of them. This form commences usually in an insidious manner before the second dentition, although in exceptional cases the onset is acute. There is a progressive enlargement of the joints, the wrists, fingers, knees, toes, and cervical spine, being the articulations most frequently attacked. The enlargement is mainly periarticular and the effusion as a rule is inconsiderable. The muscles waste and contractures are not uncommon. One feature is an enlargement of the lymphatic glands, which bears a distinct relation to the condition of the corresponding articulations; and another is enlargement of the spleen, which occurs with considerable frequency. Anæmia and sweating with pyrexia are further symptoms, and although heart disease is perhaps exceptional, an adherent pericardium has been found more than once after death; and in other cases during life endocarditis has been detected. They run an inveterate course. It would be premature to attempt to explain the nature of these cases, but it is certain that they are not all tuberculous.

Arthritis Deformans.—Arthritis deformans is rare in childhood. Some writers consider the arthritis just described as a form of this; but, in addition, cases occur in which there are lipping and bony outgrowths, and in which the muscular wasting is extreme, and yet the heart escapes. Arthritis may occasionally be a prominent symptom in posterior basic meningitis. The results of lumbar puncture may give the diagnosis.

2. **In Adults.**—*Arthritis* deformans and *gout* sometimes cause considerable difficulty.

In arthritis deformans the marked implication of the smaller joints, the intractable course, the failure of salicylate treatment, the muscular wasting, and the rapid acting of the heart (which is generally free from organic disease), are some of the main points relied upon for diagnosis. All the points of differential diagnosis are open to criticism, for arthritis deformans is an ill-defined malady.

Gout.—The differential diagnosis between acute rheumatism and acute gout is generally easy. Gout is more usual over thirty. The frequent implication of the great-toe joint and frequent escape of the larger joints, the occurrence of tophi, and the absence of heart disease, are striking differences. The habits of the patients are also suggestive. Between subacute rheumatism and subacute gout the difficulty may be great, and until gout is better understood it must remain.

Gonococcal arthritis may lead to error. It is more liable to follow gonorrhœa in those who have suffered from rheumatism or are of rheumatic parentage, and this increases the liability to mistakes in diagnosis. The history of urethritis is a cardinal point. The arthritis is exceedingly stubborn, the planter fasciæ are frequently implicated, and iritis is much more liable to occur than in acute rheumatism. The heart is less liable to suffer, and the salicylates have but little influence.

In adults and in children *influenza* may cause difficulty. The severe pains and dilatation of the heart in themselves are liable to cause confusion, and the frequent occurrence of a sore throat adds to the similarity. Arthritis also is not very uncommon as a result of influenza. In the majority of cases the onset of influenza is more abrupt than that of acute rheumatism, and

when the onset of the latter is more acute than usual the multiple arthritis develops rapidly. On the other hand, the arthritis of influenza is usually a late result.

Pyæmia with suppurative arthritis, both in adults and childhood, may be most difficult to distinguish from acute rheumatism. The difficulty is particularly great in some cases that follow acute otitis media. In these it must be admitted that acute rheumatism and the suppurative diseases approach one another very closely. Their comparative rarity, however, compared with the frequency of acute rheumatism, only serves to strengthen the view that rheumatism is specific. The prostration and general poisoning are more profound in pyæmic arthritis. Foci may form in the subcutaneous lesions and break down into small abscesses. Rigors and a high fluctuating temperature are further warnings. The heart becomes rapid and feeble, and although endocarditis is not so frequent as in acute rheumatism, suppurative pericarditis may supervene most insidiously without the appearance of any pericardial friction.

Scarlatinal arthritis is so closely allied to acute rheumatism, exhibiting as it does such manifestations as multiple arthritis, endocarditis, pericarditis, nodules, and chorea that to distinguish them is hardly possible. They may eventually prove to be identical, and in any case are so alike that their differential diagnosis is unimportant. There is certainly the same danger of future attacks.

Some cases of adynamic rheumatism and *typhoid fever* with arthritis are much alike: the occurrence of diarrhœa, splenic enlargement, rose spots, and a positive Widal reaction, are important distinctive features.

Malta fever differs in the occurrence of sudden outbursts of pyrexia with severe prostration, alternating with intervals of comparative health. The micrococcus melitensis gives a definite serum reaction (Wright).

Acute rheumatism in one joint may be mistaken for *a sprain*. This is a provoking yet not very uncommon error, which may become ludicrous when the diagnosis is upheld in spite of the appearance of a "sprain" in the other ankle.

Hæmophilic Arthritis.—The sudden hemorrhages into the joints in hæmophilia must be distinguished by their abrupt onset and by the family history. There is, however, some mysterious connection between acute rheumatism and hæmophilia, and the arthritis met with in hæmophilics is not always due to hemorrhage into the joints.

Prognosis.—The prognosis of acute rheumatism is a complicated matter, and often the attempt at prophesy is a failure, or is at the best suggestive of the Delphic oracle. It is concerned with estimating the danger to life in a particular attack, the general outlook for the future of the patient, and the liability to recurrence.

1. The danger to life in a first attack of acute rheumatism is not great. Hyperpyrexia is generally accepted as the most dangerous complication, and it is not possible, if this supervenes, to foretell what will be the issue, for some recover while others die, however prompt the treatment. Acute carditis may prove fatal in a first attack, and its occurrence in a young and delicate child of rheumatic parentage points to caution in the prognosis. It is exceedingly rare for chorea in itself to prove fatal through the violence of the movements, insomnia, and inability to take nourishment; yet this may occur. Experience, however, shows that an error in prognosis is more

likely to occur on the side of overrating than underrating the danger in uncomplicated chorea. The occurrence of the malignant type of rheumatic endocarditis in puerperal or pregnant women is fatal, and death may follow rapidly in pregnancy without any indication of a "septic" infection.

2. In judging of the outlook for the future, the *age* of the patient stands first. In general, the younger the patient the greater liability there is to further attacks, and to cardiac complications. The surroundings are also important; the child of poor parents who is living in an unsuitable climate and is badly fed and clothed is heavily handicapped. The nature of the attack is another consideration. The insidious form in the young, in which one manifestation appears after another, with the illness lasting for weeks and months, is most unfavorable. Carditis under six years of age with rare exceptions means the ruin of a life. Combined valvular lesions in childhood are also very serious. The arthritis generally ends in complete recovery, although if there is considerable periarticular swelling this recovery may be delayed and troublesome stiffness remain for some months afterward.

3. In calculating the chance of another attack the age is important, for the younger the patient the greater the liability. A strong family history of rheumatism points to an increased liability, and if the circumstances or occupations are unsuitable the danger of more than one attack occurring is enhanced. The physician will often find it difficult to say whether the symptoms are the result of a new infection or are the result of a fresh outbreak of a slumbering first infection.

Treatment.—The treatment, although in some respect encouraging, is on the whole unsatisfactory. Articular rheumatism may, it is true, respond to treatment with salicylate of sodium in a way which is almost magical; but cardiac complications in childhood are the despair of the physician.

The subject divides itself into three parts: (1) The preventive treatment. (2) The treatment of the disease itself. (3) The management of those who have inherited a tendency to the disease.

Prophylactic Treatment.—Acute rheumatism must be prevented as far as possible, yet the prophylaxis seems hardly to have appealed to the medical profession sufficiently. The resigned acceptance of the fact that hundreds of young lives are damaged by rheumatism contrasts vividly with the extraordinary efforts that are made to prevent tuberculosis. The incidence on the poor is so marked that there can be no doubt that much acute rheumatism is preventable. All teachers should be acquainted with the early signs of chorea, for we are repeatedly assured that children suffering from this disease have for some time worried over the schoolwork, and the attack is thus intensified. School-rooms should be well ventilated, and, difficult though it may be, every effort should be made to prevent children sitting in damp clothes and shoes.

Nothing but good can result from investigations into the housing of the poor and from continuous efforts to improve their habitations; for, whatever views may be taken upon the broad general question of the relation of damp to acute rheumatism, there is good clinical evidence to prove that a rheumatic patient living in a damp house will drift from bad to worse. Acute rheumatism, it will be remembered, is an urban disease. Epidemic outbreaks and the vagaries of climate are beyond our control; but much can be done by judicious advice to put parents or patients upon their guard against the dangers of rheumatism during the changeable seasons. The influence of the

nature of the soil upon the incidence of acute rheumatism is another point of interest in prophylaxis. A cold clay soil appears to favor the occurrence of the disease.

Management of the Acute Attack.—When an adult is attacked it is a great advantage to have two strong nurses, for these patients are extremely helpless and difficult to move. If possible a bed should be chosen of sufficient breadth to be comfortable to the patient, but sufficiently narrow to make it possible to manage him with ease. For the same reason it should be of a convenient height. The sick-room should be airy, but care should be taken to protect the patient from drafts—a point which is sometimes overlooked in hospitals but is nevertheless an important one in the management of acute rheumatism. If there is profuse sweating the patient should be between soft blankets, but unless this is the case (and it is not usual in childhood), it is much more soothing to be between sheets, in a light flannel nightdress. The perspiration should from time to time be sponged off with a warm sponge, and the patient dried with a soft towel. It may be necessary to keep the bedclothes from the tender joints by a cradle.

While the disease is acute the diet should be fluid and mainly non-nitrogenous, for there are good reasons for believing that the renal functions are impaired during the acute phases of rheumatism. In the lingering subacute type with carditis in children it is frequently advisable to allow as nourishing a diet as can be taken. Thirst can be quenched with lemonade, barley-water, or plain drinking-water.

Medicinal Treatment.—At the commencement of the attack the bowels should be opened. Calomel in a dose of 2 grains (0.13 gm.) followed by a saline generally answers admirably. Severe purging is unnecessary, and if the bowels are obstinate throughout the attack cascara or senna is suitable. *Alcohol* is not as a rule required, unless for some special crisis such as acute cardiac failure or hyperpyrexia. It is, however, useful in case of asthenic rheumatism in which the tongue is dry and the prostration considerable. *Bleeding* has gone out of fashion, to the advantage of the patient, for rheumatism is a disease which seriously impoverishes the blood. If the throat is affected a chlorate of potash and salicylate gargle should be employed if feasible.

Local applications to the joints are often of service. Warm cotton wool in most cases answers all purposes, with oil of wintergreen, belladonna and opium liniment, or warm alkaline lotions. In some cases the pain in one joint may be exceedingly severe and persistent, and it is then advisable to fix it with a splint.

Of internal remedies the salts of salicylic acid first require consideration. Some maintain that these are true specifics, and go so far as to consider that symptoms which do not yield to them are not rheumatic in nature. If this view is a correct one these drugs are indicated in all forms of acute rheumatism, whether articular, cardiac, pulmonary, or nervous. Experience, however, has amply shown that their effect upon cardiac rheumatism is very feeble as compared with their effect upon articular rheumatism, and in explanation of this two reasons are advanced—that the drugs are not sufficiently pushed, and that the patients come under treatment at too late a stage. Unfortunately the fundamental statement that the salicylates are a specific remedy is not established; and a further question arises: Can they be pushed without detriment to the patient? It is clear that if the reason for

their employment is not an absolutely sound one it would be unwise to push them if they are in themselves deleterious. Again, even if salicylates are specific, we do not wish to exclaim with the French surgeon, "Messieurs, Il est mort—guéri."

In the writer's judgment large doses of sodium salicylate are detrimental, and in cardiac rheumatism, especially, are liable to introduce new dangers and in critical cases may turn the scale against the patient. It is a difficult question, on the other hand, to decide whether these drugs prevent cardiac rheumatism if they are given before it is detected. This can be asserted, that rheumatic manifestations—for example the nodules—may appear even when large doses (*e.g.*, 15 grains of sodium salicylate every four hours to a child of ten) are being given; and also that in spite of the widespread use of the salicylates, cardiac rheumatism is very frequent.

The ill effects of large doses of these drugs are general depression, a small pulse which is sometimes irregular or slow, vomiting which may be most difficult to arrest, deafness, dizziness, buzzing in the ears, delirium, and occasionally irritation of the kidneys. The gravest and most remarkable of all are respiratory disturbances. In some cases dyspnœa supervenes, with breathing like that seen in diabetic coma and the patient may collapse and die within twelve hours. These dangerous symptoms or severe vomiting may appear after a few large doses—*e. g.* 20 grains—to a child of eight years. There is no doubt that sodium salicylate has been much improved in purity since its first introduction, yet in spite of this it is in large and continuous doses essentially a depressant. In writing thus, the reader will clearly understand that the opinion expressed is neither original nor, on the other hand, by any means universally accepted.

The treatment of the articular form of rheumatism is much more encouraging, and in very many cases the salts of salicylic acid answer admirably. The treatment is more easily borne if the bowels are first opened by an aperient; and the particular manner in which the drug is administered will vary with the character of the case. If the patient is a strong adult, 20 grains (1.3 gm.) of salicylate of soda can be given in combination with 20 grains of bicarbonate of soda and 20 minims of tincture of ginger, in 1 ounce of chloroform water every three hours, for four doses, then every four hours, later every six hours, and lastly three times a day. Where there is much distress and insomnia it is advisable to give a sedative in the evening. A patient with a feeble circulation will bear the treatment better if the aromatic spirits of ammonia are combined in 15 to 20 minim (1 cc.) doses, and if some brandy is given occasionally. Salicin is advisable for the delicate, and especially for delicate children, and the natural salt is still the safest form of salicylate.

When the temperature has fallen it is advisable to persist with salicylates in diminishing doses for at least a fortnight, rather than to leave them off abruptly. This is a general rule; the physician, however, will be guided by warning pains and by the temperature chart in the management of the patient during this stage. A useful combination, after the disease is controlled, is salicylate of quinine; and from this during convalescence a change can be made to quinine, which can be prescribed for the adult in an effervescing solution.

If the heart is not damaged and the course of the illness has been favorable the patient may be convalescent in three weeks. Relapses or recrudescences are, however, frequent, and a too liberal diet or too early return to active

movement is generally blamed for them. It is, however, very doubtful whether a careful increase in the range of diet, such as is suitable to any convalescent, can be responsible for their recurrence. Active movement is more probably a factor, for there appears to be a decided tendency for all rheumatic manifestations to gain ground if adequate rest is not given.

It is a useful precaution to have the joints and limbs that have been attacked, massaged and exercised by passive movements before voluntary movements of any considerable extent are undertaken; the tissues are thereby stimulated to complete recovery before the strain of voluntary movement is thrown upon the softened ligaments, swollen synovial membranes, and weakened muscles. At this stage a stimulating liniment is also helpful, such, for example, as the compound camphor liniment, or compound mustard liniment. The strength of these will be graduated according to the susceptibility of the patient's skin.

Convalescence often finds the patient very stiff and the muscles wasted and painful. It is then that hydropathic treatment is of much service, and restores the patient's strength and muscular firmness. It is doubtful whether there is any remarkable virtue in the waters themselves, and sometimes also there is no special advantage in the locality; but the well-organized arrangements for systematic stimulation of the joints are most valuable when the disease itself is dying down and yet recovery is slow. It is said sometimes by patients and by their doctors that the locality and this treatment first brings the rheumatism out of the system; but it is much more probable that then there has been a relapse at the spa comparable to the relapses which may occur at home.

In some cases apart altogether from carditis there may be troublesome complications. One of these is the persistence of the inflammation in one or two of the joints. This is to be feared when there is excessive tenderness, much redness, and periarticular swelling. Salicylates have no influence over this condition, and the erroneous diagnosis of a gonorrhœal arthritis is sometimes made on this account. If the joint is opened, clear or blood-stained fluid exudes from the connective tissues and cavity. The patient should be warned that recovery must be slow, and may possibly be imperfect. In the acute stage the joint should be fixed by a splint, and a plaster of Paris case is very useful if it is made in such a way that it can be easily removed. A generous diet and plenty of fresh air are valuable adjuncts to the treatment of this troublesome complication. An occasional blister relieves the pain and sometimes does a great deal of good to the joint, although the explanation of its action is difficult. As soon as a light massage can be tolerated it should be employed, and later combined with gentle passive movements. Douching and skilled massage are invaluable when the patient can bear the treatment.

In other cases one joint remains obstinately distended with fluid, and here again good food, fresh air, and quinine, are more successful than the salicylates. Blisters are often very useful in promoting absorption. If in spite of prolonged rest and counterirritation by strong liniments, blisters, or the cautery, the joint remains distended with fluid, then skillful strapping with Scott's dressing (Ung. Hydrargyri Co.) is indicated. The strapping should be tightened from time to time, and the joints kept at complete rest. If this fails, aspiration and flushing with 1 per cent. carbolic acid solution is valuable; after this the joints should be carefully and firmly bandaged, and if there is any suspicion of active rheumatism full doses of salicylate of soda

should be given during the next few days. In all operations upon the joints in rheumatism it must be remembered that the primary location of micro-organisms is in the subendothelial tissues and not in the arthritic fluid.

Dry heat in the form of the radiant heat baths has been strongly recommended and is a valuable stimulant. There are no certain indications for its use, and it may, as all other measures do, fail in the thoroughly bad cases.

Iodide of potassium (gr. v, gm. 0.3) with salicylate of soda (gr. xv, gm. 1) often relieves the articular pains, which are worse at night. This nocturnal suffering is most distressing to the patient, and for this reason the above combination is always well worthy of trial, though unfortunately it is not always successful. This method of treatment can be well supplemented by a nightly dose of the lead and opium pill.

A considerable number of different preparations of the salicylate compounds are now in the market. Among the better known are aspirin or salicyl-acetic acid, saloquinine-salicylate or rheumatin, and salophen (acetyl-para-amido-phenyl-salicylic-ester). It is claimed for aspirin that it is pleasant to take, not a cardiac depressant, and not liable to cause gastric disturbances. It is certainly well tolerated, both by adults and children, but vomiting and depression will occasionally result from large doses, as with salicylate of soda. In adults it is prescribed in dose of grs. x to xv (0.65–1 gm.). Some prefer to prescribe this drug both for adults and children in water acidulated with lemon-juice. Salophen, which contains over 50 per cent. of salicylic acid, is also prescribed in doses of from 10 to 30 grains. Rheumatin is useful when the attack is subsiding, and as a preliminary to more tonic treatment. The dose for an adult is 15 grains (1 gm.); for a child 5 to 10 grs. (0.3–0.61 gm.), repeated three times a day.

The alkaline treatment has been superseded by the use of salicylates, although some physicians still find good from full doses of potassium citrate with potassium bicarbonate.

The tonic treatment of the convalescent needs some care. The anæmia that so often results requires iron. Arsenic is also useful, and may be given as Fowler's solution combined with alkalies, and the ammoniated tincture of quinine. For children cod-liver oil is often very useful, especially when they are thin. A dry inland climate is best for those of vigorous constitution. The feeble, delicate, rheumatic convalescent does better in a dry and mild climate.

Serumtherapy.—The idea of treating acute rheumatism with some curative serum is one that of late has come considerably to the fore. It is essential to keep in mind the possibilities and the dangers of such a method. The very character of the disease makes it one about which it is most difficult to arrive at a conclusion as to the value of any method of treatment. Rheumatic chorea especially is most uncertain in its course, and numerous observations by many different physicians are requisite before any conclusions can be drawn. The antistreptococcic sera in use are antibacterial, very uncertain, and cannot as yet be standardized. Those, however, who believe that acute rheumatism is an outcome of any streptococcal infection have hopes that a polyvalent serum made from various strains of streptococci may do good. In our present ignorance of these most complex poisons and antidotes who can deny this? The believer in the specific character of rheumatism also cannot deny that other microörganisms allied to that found in acute rheumatism may possibly form in some degree allied or similar poisons,

and must admit that such a serum may possibly do good. The position is nevertheless an unsatisfactory one around which much error and faulty treatment may arise.

The writer had no success with such a serum in six carefully chosen cases, but Menzer has reported some successes with a serum manufactured by Merck. Menzer's serum produces very definite effects in subacute cases. After four to six hours, redness, swelling, and heat, occur in the affected joints but in no others. For a time the cardiac symptoms also appear to be augmented, there are fever and pains in the neck and head, swelling of the lymphatic glands, and sore throat. Later there is a fall of the temperature by degrees, and then cure. His successes have been more signal with chronic than with acute rheumatism. The dose must be gauged by cautious use, the test dose being 5 to 10 cc. As much as 200 cc. have been used for a single case. Up to the present discordant results have been obtained with this serum, and the local reactions are somewhat disturbing.

The treatment of rheumatic heart disease is too extensive a subject to be dealt with in this article, but a few points will be touched upon. The pain of pericarditis is much relieved by an ice-bag applied to the precordium. Continuous application is the most satisfactory. Unless there is painful arthritis the writer trusts to quinine, strychnine, opium, digitalis, and stimulants, rather than to the salicylates. In exceptional cases when the right heart is acutely dilated venesection is called for. Rheumatic pericarditis may be overtreated, and the patient be more harassed by measures for his relief than by the disease itself. Paracentesis in pericarditis should not be attempted until there is very definite proof that the embarrassment of the cardiac action and the great enlargement of the area of dulness are not results of acute dilatation of the heart.

Rest in all forms of rheumatic heart disease is of first importance, and the guides for relinquishing it will be the rate of the pulse, the size of the heart, and the absence of breathlessness upon the resumption of active movement. Passive movements and massage are valuable introductions to more strenuous exertion.

"Cerebral rheumatism" with hyperpyrexia requires prompt treatment with the cold bath. The cerebral symptoms are even a better guide than the temperature for its employment. A temperature of 105° F. in acute rheumatism is a signal of danger. A temperature of 104° with headache and vomiting is of equal significance if there are no local lesions to account for it. The bath should be given at a temperature of about 85° F. and rapidly cooled by putting in blocks of ice. The patient is watched throughout with the utmost care, and the duration of the bath graduated by his strength and by the effect upon the temperature. If there is collapse he must be at once removed, rapidly dried, and wrapped in warm blankets. If his temperature falls in the bath—from 107° to 102° F., for example,—the patient should be removed, for the temperature will fall to normal after leaving the bath. Stimulants are needed and should be close at hand, but depressant antipyretic drugs are not advisable. The bath may need repetition several times in a severe case. If a bath cannot be given, ice sponging with cold packing may save life.

The Management of Those Predisposed to Rheumatism.—Careful attention should be paid to the warnings of rheumatism in children of rheumatic parentage, and the throat should be promptly treated if there is a tendency to tonsillitis. Among the wealthier classes the possibility of an

unsuitable house or climate should be carefully considered. Nervous, intelligent, rheumatic children should not be pressed at school work, and evening study often does them harm. When they are thin and irritable, enforced rest in the middle of the day is advisable, and it is remarkable how useful such a simple remedy as rest often proves to be in those of rheumatic predisposition. Woolen or wool and silk garments should be worn next to the skin, and if an attack of acute rheumatism has occurred and the climate is cold and inclement, it is advisable to winter in a dry and bracing atmosphere.

CHAPTER XXVI.

ASIATIC CHOLERA.

By W. P. DUNBAR, M. D.

History, Epidemiology and Etiology.—The oldest known description of cholera seems to be that of the Hindu Sucruta. In this the following symptoms are emphasized: diarrhœa, vomiting, thirst, stabbing pain, and coma. "A man whose teeth, lips, and nails are blue, whose consciousness is impaired, who is tormented with vomiting, whose eyes are deeply sunken, and whose voice is weak and joints relaxed;" so reads the literal translation of Justis.

It was once believed that the name cholera was derived from the Greek word χολή, "gall," but others have thought that the Greek word χολάς, "intestine," was the origin. Still others believed that it rose from the Hebraic expression, choli-ra, an evil disease. In recent times the opinion has prevailed that it is derived from the Greek word χολέρα, an eave-trough. The dejections stream from the intestine like rain from an eave-trough.

Cholera Asiatica occurs in the form of epidemics which, following the paths of human traffic, spread quickly over wide areas and carry off 50 to 55 per cent. of those affected. No disease showing these features, and at the same time presenting a definite tendency to epidemic distribution, appeared in the civilized world, certainly not in Europe and America, before the beginning of the nineteenth century. Such an epidemic, starting in India in 1817, spread eastward to China and Japan and westward it reached, in 1823, as far as Russia (Astrakhan). Some years later it again spread over great tracts of India, and travelled westward over Persia and Arabia to Russia. In 1831 it reached as far as the eastern districts of Germany. In 1832 it spread over the western part of Europe, through France, the Netherlands and England, whence by ships it was carried to Canada and extended to the State of New York.

Since then it has repeatedly encircled the earth; scarcely a country has escaped. Only such regions as are reached from India by a long sea trip, such as Australia and Cape Colony and the unfrequented regions of the Arctic Zone, high mountainous districts, etc., remained free. The origin of epidemics has always been India.

As to how long cholera has been known in India itself, a complete unanimity of opinion has never been reached. The first European that came to India is said to have found it as an endemic, partly epidemic, disease. A great epidemic in Goa in 1543 was reported. Koch has gained the impression that the reports on the cholera epidemics before 1817 are not trustworthy. On the other hand it is regarded as proved that in the sixteenth, seventeenth, and eighteenth centuries outbreaks of cholera certainly occurred in India.

In any case, the real home of cholera lies in India and more precisely in the lowlands of the southern parts of Bengal with Calcutta for the chief city.

This is the region traversed by the Ganges. Here cholera prevails continuously and, as a rule, is most severe in the hot dry month of April. The climate of this region is characterized by heat and great moisture. From here the cholera spreads out, almost the whole year round, over larger or smaller parts of India; and from here have begun the great epidemics.

According to Hirsch, four pandemics are to be distinguished up to the year 1875. The first lasted six years, from 1817 to 1823, and extended over Asia and Africa only. The second lasted eleven years, 1826 to 1837, the third from 1846 to 1862 and the fourth from 1864 to 1875. These last three pandemics extended over all the four great continents. The fifth pandemic began in the year 1883 and lasted until 1896 (thirteen years). The sixth pandemic began in 1902 and reached Egypt, Persia, Russia, and Turkey. In the year 1904 it began to extend into the interior of Russia, where it remained during the winter. The question is of great interest whether by modern methods of combating the disease it will be possible to limit it or whether we must reckon with its further wandering in the accustomed way. In 1905 the disease was introduced into Germany from Russia, 100 workers on river-boats having cholera, but there was a total of only 254 cases in Germany, no place having more than 2 or 3 cases. In 1906 no cases occurred in Germany, which shows the benefit of energetic measures against the spread of the disease.

Haeser regards the two great pandemics of Hirsch as one pandemic with subdivisions, and introduces between the third and fourth of Hirsch's pandemics one which lasted from 1852 to 1860. It is generally agreed that cholera, following always the principal paths of human intercourse, has spread from point to point with greater rapidity as the rate of transport has increased. It has followed the course of shipping as well as that of traffic by land. With changes in the paths of traffic the route of cholera changed also. The construction of the Suez canal affords an instructive example, as, after its opening, the movement of cholera underwent a profound change. The wanderings of the disease make it clear that the cause is not indigenous but only after it has been introduced from the outside can it begin its great activity. But some held that there was no need of the invasion of a definite infectious agent and were known as Autochthonists. They were opposed by the Contagionists, who held the opinion that cholera was transferred from man to man without any intermediate link. As a variation of the Contagionists' conception one may consider the so-called "drinking water theory," according to which the use of water which has become polluted by the dejecta of cholera patients can give rise to outbreaks of cholera. By bringing forward water as a vehicle for the transmission of cholera it was thought that an explanation might be offered for the explosive outbreaks which are so characteristic. The very first appearance of cholera in Europe gave occasion for examination for the cause. The blood of the patients and especially the stools were investigated, and the most fantastic structures were described as having been found. Small motile creatures of the form of vibrios were observed and regarded as identical with the vibrios noticed by Leeuwenhoek in dysentery. Further microörganisms in great variety were described in the vomitus as well as in the stools.

The cholera expedition sent to Egypt in 1883, under Koch, found in Alexandria an opportunity to study 11 living cholera patients, and the cadavers of 10, a few hours after death. The investigation of the intestine

showed in all cases (with the exception of 1 which ended fatally as the result of a secondary disease several weeks after the recovery from cholera), the presence of a definite organism. The results, however, did not allow of a positive conclusion by the time the epidemic was over. On Koch's suggestion the expedition was sent to India to continue investigations there and they succeeded in making pure cultures of the organism. The investigation of 42 cholera cadavers and 28 cholera patients resulted without exception in the confirmation of the findings which had been reached in Egypt. On the other hand these bacteria were completely lacking in 28 cadavers of persons who did not have cholera. It was always possible, both from all cholera corpses as well as from the dejecta of the cholera patients, to isolate a quite characteristic comma-shaped bacterium, a vibrio.

In addition, the commission examined the bodies of animals, sewage, swamp mud, and river water. It was never possible in a single instance to find the vibrio. Koch concluded that his comma-shaped bacteria were peculiar to cholera. The question as to whether these were merely favored in their growth by the cholera process and were therefore conspicuous when associated with cholera Koch thought he might answer in the negative. Accordingly, one possibility only remained; namely, that these vibrios were the cause of the disease.

In spite of the force and clearness of Koch's proofs, there were, not only among the laity but even among physicians, very numerous adherents of the localistic theory. The fact that this theory rejected all quarantine, isolation, expensive disinfection, etc., in the combating of the disease made this doctrine especially popular and gained a ready hearing in circles which were interested in commerce. When, in the year 1892, the cholera appeared in Hamburg suddenly and without warning and in a few weeks, out of a population of about 600,000, attacked almost 17,000 and carried off 8,600, the whole civilized world was aroused and naturally all possible means were used to arrive at a definite solution as to its cause and mode of spread. It was not the fact that in European Russia this same pandemic destroyed 800,000 men, which aroused the public. That cholera could gain such a firm footing under the unhygienic conditions in Russia and could spread was considered inevitable. It was to be expected of Germany, however, that cholera should be unable to gain a footing. Here, as in England, people hoped that a highly developed civilization would be sufficient to rob such a pestilence of its malignant character.

Hamburg was indeed the first city on the continent which had fulfilled the requirements of the Localists and provided itself with a model sewerage system. Five decades of drainage of a soil protected from every sort of defilement, should according to the doctrine of the Localists, have brought about in the subsoil a perfectly sanitary condition. The localistic doctrine must be regarded, since the experience of Hamburg, as completely disproven. On the other hand, the Hamburg epidemic, with the consequent invasion of 269 places in Germany, furnished an overwhelming burden of evidence of the correctness of Koch's doctrine. The explosive outbreak of the Hamburg epidemic reached its climax in ten days with more than 1,000 new cases daily, and within nine weeks reached its termination with the exception of occasional sporadic cases. The field overspread by the cholera corresponded precisely with the Hamburg water supply, which then came from a point in the Elbe to which the sewage of the city was carried back by the tide, and

this infected river water was still pumped into the water mains unfiltered and without any effort at purification. The cholera had no such distribution in Altona, which lay to the northwest; there only relatively few cases appeared which could be referred to transportation from Hamburg. In the opposite direction, Wandsbeck, with 20,000 inhabitants, although in direct communication with Hamburg, remained free from cholera with the exception of a few cases transported from Hamburg.

Pettenkofer sought to rescue his localistic doctrine by declaring that the Hamburg subsoil was much defiled by the years of sprinkling of unfiltered hydrant water. This hydrant water would not be injurious according to his view if directly ingested, but would be sufficient to poison the ground and subsoil. We have really no reason to speak well of the Hamburg water supply as it was up to the year 1893, nor to say from a hygienic point of view it was free from objection. But it must not be forgotten that still only a very small part of the city sewage ever reached the part of the river from which the water was drawn; and this occurred not every day in the year but only when the water was low in the Elbe, or after storms. Furthermore, Reincke has shown that the cholera did not appear only in the older and low lying parts of the town, but that it raged with the same intensity in the higher parts which had but recently been built and whose ground was not infected, because building had not been allowed in this neighborhood until the sewage system had been completed.

That the cholera in Hamburg was actually distributed by hydrant water, and that infection took place by its use is clear from the fact that those institutions which did not use the city water but had their own wells remained completely free. Those parts of Hamburg where wells were exclusively used did not suffer, while those districts which used both the wells and city water were affected much less severely than the remainder of the town.

From Hamburg cholera was transported to 268 other places. The government sent out trained men to these places, who, basing their ideas on Koch's theory, ordered the necessary precautions. In all these places together, excepting Hamburg, not more than 800 persons succumbed. In the year 1893 there were again 114 different places in Germany visited by cholera but in all only about 300 persons died. Although Germany was especially threatened from Galicia and Russia, the pestilence did not succeed in gaining a foothold because suspected individuals were carefully guarded and special care was taken that no water suspected of infection was used. In the year 1894 the cholera gained entrance again into 157 towns of Germany but only 490 persons in all died of the disease. In the year 1895 no cholera appeared in Germany. The epidemic thus ended in three years, while earlier epidemics had lasted an average of ten years.

Everywhere the cholera appeared, the organism described by Koch was found. His theory was thus most brilliantly confirmed. According to it the infectious agent occurs in the dejecta of the cholera patients, and is usually transferred to others by objects which become infected. Especially important is polluted water. According to Koch transportation by the air never occurs. Through these discoveries cholera lost most of its earlier terrors. Koch asserted that he never claimed that everyone who took in the cholera parasite would suffer from a uniformly severe attack of cholera. Although we had recognized the cholera vibrio as the true cause there were nevertheless

a number of accessory causes, such as conditions of locality, time, and individual predisposition.

The Cholera Vibrio.—Morphology and Cultural Characteristics.—The bacteria are about 1 to 1.5μ long and 0.3 to 0.5μ thick. They are not quite straight but slightly curved like a comma and this curvature may be so great that the rod takes the form of a semicircle. In pure cultures these rods often form S-shaped figures and longer and shorter wavy lines, of which the first represents two individuals and the latter a larger number of cholera bacteria which have remained connected after a continued multiplication. They possess independent motility which may be best observed in a hanging drop. In such a preparation the bacteria are to be seen moving with great rapidity in all directions. One may recognize in such a preparation that the apparently wavy lines actually represent delicate spirals.

Especially characteristic is their behavior in nutrient gelatine, in which they form colorless colonies which, with low magnification, resemble after twenty-four hours bubbles which are not quite circular but show an irregularly partly scalloped contour. Very soon they assume a somewhat granular appearance, which comes out more sharply in the large colonies, until the latter seem as if composed of highly refractive granules, which Koch compared to little heaps of particles of glass. With further growth the gelatine liquefies in the immediate neighborhood of the colony and the latter sinks somewhat deeper into the gelatine. It forms in this way a small funnel-shaped depression in the middle of which the colony is visible to the naked eye as a whitish point. The liquefaction of the gelatine never extends very far in the neighborhood of the colony (provided that the colony is isolated enough), a property which distinguishes the colonies of cholera bacilli from many others which liquefy gelatine. The macroscopic appearance of a gelatine plate, which contains numerous young colonies of cholera bacteria lying close together, is also characteristic. The surface of the gelatine resembles in this case that of a ground glass plate. Often in consequence of the very slight difference of level which is caused by their sinking into the surface of the gelatine the young colonies show a reddish appearance in certain lights.

The size and form of the cholera vibrio varies somewhat. In some cultures they show a length of 1μ while in others they are about 3μ. Certain strains show quite short curves with very little twisting, while others are very much twisted. The cholera vibrio takes up basic aniline dyes well. It is completely decolorized by Gram's solution. Staining methods have been proposed to give a specific reaction to bring out a capsule, a membrane, or bright spots, but these have never gained any practical importance and now it is generally recommended to stain with diluted Ziehl's fuchsin solution (1 to 9).

According to Koch's first description the cholera vibrio is provided with only one terminal flagellum. Later observations were published describing cholera vibrios bearing several terminal flagella. Kolle and Gotschlich have recently had an opportunity to study 65 different cholera cultures with regard to this point. All the colonies showed, without exception, only one terminal flagellum. As regards the size, length, and waving of the flagellum, however, there were definite differences. These authors found in certain vibrios which were otherwise very similar to the cholera vibrio, various types in which several terminal flagella were present and in one case there were also lateral flagella.

Gelatine and Agar Cultures.—For years gelatine plates have been almost exclusively used in the isolation of cholera vibrios but investigations have shown that the growth does not always occur on gelatine plates in the typical way described by Koch, but that considerable variations may occur. Nevertheless these do not make the gelatine plate deceptive for diagnostic purposes and even the most atypical cholera colonies are easily distinguished from the intestinal bacteria which are commonly found. It is a drawback that the growth goes on quite slowly on gelatine plates, because cultivating the plates at a higher temperature than 23° C. must be avoided.

Various mixtures of agar and gelatine have been proposed which might allow the characteristic growth of gelatine plates together with the possibility of a more rapid cultivation. It has, however, proven simpler and just as effective to use ordinary agar plates. The fluid agar is allowed first to solidify in the Petri dishes and then to stand from one-half to one hour in the thermostat at 37° C., or five to ten minutes at 60° C., in order to evaporate the water of condensation. The surface is then smeared with the material to be investigated. Dilutions may be produced by smearing one after another the surfaces of several plates with the same material. The use of agar to which 10 per cent. of blood is added, is of value.

The colonies of cholera bacilli developing on the surface of the agar are brighter and more transparent in reflected light than the colonies of ordinary intestinal bacteria. One frequently observes in the colonies of cholera organisms a margin, or ring formation, but the growth of these colonies is not so characteristic as on the gelatine plates. It is, therefore, advisable to transplant several of the suspicious colonies for further investigation. Although the result can be reached more quickly with agar than with gelatine plates, one should nevertheless inoculate the latter at the same time. There are cases in which the gelatine plates lead more surely to the desired result. This is especially true of the investigation of suspected drinking water.

Methods for Accelerating the Growth.—With the appearance of a disease suspected of being cholera, it is important to make a diagnosis as quickly as possible and efforts were made to discover conditions more favorable for the increase of the cholera than for other bacteria. Schottelius pointed out, in 1885, that the cholera vibrio is highly dependent on oxygen and therefore accumulates rapidly at the surface of fluid cultures. If, therefore, cholera dejecta are covered with bouillon and put in a warm place, the cholera vibrios can be found in masses on the surface of the culture after ten or twelve hours. In the Hamburg epidemic of 1892 the writer observed that the cholera vibrio found particularly favorable conditions for growth in peptone solution which was inoculated with the cholera dejecta for the purpose of developing the cholera red reaction, and soon collected on the surface in the form of a scum, as described by Schottelius. The writer repeatedly succeeded, in cases where plate cultures failed, in cultivating the vibrios by inoculating gelatine or agar plates from a solution of peptone which had been inoculated with dejecta and kept for three, six or nine hours at 37° C. The Elbe and hydrant water were studied in a similar way, and, while other attempts by direct inoculation of plates failed, the writer succeeded in a number of cases in obtaining the bacteria from suspected water. Koch at once took an active interest in this method, but he has never claimed to be its discoverer. Nevertheless, it is given his name by some writers.

An especial advantage in this method is the fact that larger masses of infectious material can be investigated, *e. g.*, several cubic centimeters of fæces. Repeatedly the writer succeeded in demonstrating the cholera vibrio in material in which the direct agar or gelatine cultures were unsuccessful. Of the suspected water even greater quantities were used than in the case of dejecta.

Resistant Forms.—The idea is at present generally prevalent that the cholera vibrio does not form resistant bodies, but it has proved itself to be much more resistant to injurious agencies than was generally thought. It is important to know how long the organism can remain alive in dejecta and infected water, and whether in the latter an actual increase can occur. It is also of great interest to know how long the cholera vibrio lives on articles of food and under what circumstances the latter can be actually infected by insects which have come in contact with cholera dejecta, and finally whether the cholera vibrio can increase in such insects.

From the fact that cholera in our latitudes spreads chiefly in late summer, the conclusion was drawn that insects could hardly be without influence. Perhaps the cholera vibrio finds at that time more favorable conditions for growth. However, in the summer more water is ingested than at other seasons and more opportunities are afforded for indiscretions in diet, which increase the susceptibility of the individual.

Cholera Vibrios in Healthy Persons.—Koch held the view that, in Europe at any rate, man must be regarded as the real bearer and reproducer of the cholera organism. Many isolated epidemics could theoretically be explained only on the assumption that completely healthy persons, or persons not noticeably diseased, had introduced the organism and so formed the connecting link. This was first confirmed by the winter epidemic in Hamburg in 1892–93, when the writer with the help of the peptone culture medium was able to recognize the cholera vibrio in no less than 28 persons who were completely healthy and besides had never suffered any symptoms of cholera or the slightest diarrhœa. The great importance of this discovery was misconstrued by many and used as the starting point for violent attacks on the Koch cholera theory.

The Length of the Stay of the Cholera Vibrio in the Intestine of the Diseased.—As a rule, living bacteria are not found longer than eight or ten days. Rommelaire found them after forty-seven days and Kolle after forty-eight days. According to this, it must be regarded as definitely established that apparently quite healthy persons may carry around for a month and a half the cholera organism in a condition capable of developing, and in that way give rise to further infection.

Duration of Life of the Cholera Vibrio in Dejecta.—Investigations have, as a rule, indicated that the cholera vibrio can live only two or three weeks in dejecta. But the writer was able to demonstrate cholera vibrios, still capable of developing, in cholera dejecta, kept at room temperature or on ice, after one hundred and sixty-three days. Such a power of resistance in a material laden with foreign bacteria, shows that the cholera vibrio can exist long enough outside the human body to explain many facts otherwise very perplexing.

Influence of Temperature.—The vital power of the cholera vibrio is far greater at medium and low than at high temperatures. Formerly it was believed that it, as a native of the south, demanded a high temperature and

that it must perish at a low temperature. Therefore it was incomprehensible how the cholera could winter among us, but the writer has preserved cholera dejecta at a temperature of about 0° C. and still found vibrios capable of developing after twenty days. It has been possible to cool the cultures to −31.8° C. without destroying the organism. Even when the cultures were alternately frozen and thawed twelve times they still contained living vibrios. Kasansky kept cholera cultures four months at a temperature between −6 and −31.8° C. without the destruction of the vibrios.

Behavior of Cholera Vibrios in Corpses and in the Ground.—In former years great importance was attached to the question as to whether infection could come from cholera graves. But it has been experimentally shown that the vibrios perish very rapidly in the bodies of those dead from cholera. The writer made extended investigations in this direction in 1892–93, but they were all negative. They are of especial interest on account of the fact that the land in which the cholera corpses were buried was drained to the depth of from 1 to 1½ meters. We investigated the drainage water and found this not only free from cholera vibrios but also almost free from any living bacteria, although the rain water passed through ground in which thousands of cholera corpses had been buried. In buried guinea-pigs which had died of cholera infection, Petri, von Esmarch and Klein, were able to demonstrate the cholera vibrios only up to the fifteenth and nineteenth days.

Power of Development of the Cholera Vibrio in Water.—What becomes of cholera vibrios when they pass into water? Until recently the view was held by many that the cholera vibrio which passed into water rich in other bacteria must be destroyed within a very short time, and that there could hardly be any question of their increase under such conditions. This is a problem of great interest. If we must change our conceptions and reach the conclusion that the cholera vibrios possess far greater powers of resistance in presence of other water bacteria or even the power of increasing in impure water, many still unsolved epidemological problems would receive a satisfactory explanation. In the writer's opinion the material already before us is sufficient to prove that, even in our climate, the cholera vibrio is able not only to persist a long time in spring and river water, but that under certain conditions it can even increase.

It may be regarded as established that the cholera vibrio does disappear rapidly in certain water, *e. g.*, according to Hankin, in the Ganges and Jumna rivers. On the contrary it seems to find in the water of the Elbe very favorable conditions for development. After the epidemic of 1892, many kinds of vibrios, whose biological characters were extraordinarily similar to those of the cholera vibrio, appeared yearly for some years in enormous numbers in the water of the Elbe during the autumn. For a series of years they were absent or found only in small numbers. In 1905, when cholera was introduced into Germany, these cholera-like bacilli were found in enormous numbers in the Elbe. In 1906 they had entirely disappeared. Haffkine has reported that he recognized in India, in the tanks in the neighborhood of which cholera had existed, abundant cholera-like vibrios, while in the tanks in neighborhoods free of cholera such vibrios were regularly lacking. In Hamburg we investigated frequently the water of the Alster, one of the small tributaries of the Elbe, without ever finding cholera-like vibrios in it.

It has been demonstrated that the cholera vibrios are capable of continued existence in sterilized water for a long time. A year after the infection of sterile well water cholera vibrios still capable of developing may be recognized. Even in sterile distilled water they exist for months. The writer inoculated unsterilized Elbe water with cholera dejecta and was able to recognize cholera vibrios still capable of developing after twenty-five days. These specimens were kept at room temperature. At the writer's suggestion, Oergel infected unsterilized Elbe water with the cholera vibrio and kept it in a refrigerator at 8 to 9° C. From this he was able after almost a year to isolate cholera vibrios capable of development. Occasionally the recognition was difficult, at other times Oergel found that the cholera vibrios were the predominant organism. The latter, under the conditions mentioned, undoubtedly increased temporarily to a great degree. Of course it is not proved by this that the cholera vibrio is able to exist as long in the free flowing water of the Elbe. Still this is made probable by these findings. Hankin also reported that he could recognize cholera vibrios in a well for longer than a year. In Hamburg in 1893 cholera vibrios capable of developing could be recognized not only in the Elbe water at various points but also in the city hydrant water. Hence it must be assumed either that the cholera vibrios had persisted throughout a whole year in the Elbe or that they had been introduced anew in 1893. In both cases an increase in the cholera vibrios in the Elbe must be assumed. If these had not been present in extraordinarily great numbers, indicating an active multiplication, it would have been impossible to recognize them at various times and at various points in the river.

In the year 1896 cholera vibrios were again successfully isolated from the Elbe water. The problem as to whether they had remained there from the year 1892 or had been again introduced was left undecided. We were able in 1893 to recognize in the Oder, where cholera had broken out, the cholera vibrios as well as in the Ruhr and in the harbor of Ruhrort when cholera prevailed there. Personally, after such findings, the writer considers it proven that the spread of cholera by water is, in our latitudes, to be regarded as dependent not only on cholera vibrios which reach the water with cholera dejecta and remain alive but also, under favorable conditions, on their increase there. The attempts to solve the problem as to whether the water in localities which have never suffered from cholera does not allow of the development of the vibrios, while that from infected localities may perhaps afford favorable conditions for their growth, require great persistence and diligence. The number of instances in which cholera vibrios, capable of developing, have been recognized in wells and other sources of water supply has increased since 1892 but they are not yet sufficient to decide the question as to the degree in which cholera vibrios are capable of increasing in river and well water.

Power of the Cholera Vibrio to Persist and Develop on Food Stuffs.—How far may the transmission of the disease take place by articles of food which are infected? Strong has reported that in Manila cholera is undoubtedly spread by articles of food. Hankin reports the transmission by cucumbers which had been directly polluted by dejecta. Instances of infection from many articles of food have been established. All the experiments have shown that the cholera vibrio lives for a relatively short time on foodstuffs. In sterilized milk they grow well, but in unsterilized milk they

are destroyed as soon as the milk begins to sour, according to Kitasato. Nevertheless, Heim was able to demonstrate living cholera vibrios in milk which had been sour for six days. Since milk comes in contact with water, not only in adulteration but in the washing of the cans, great care should be devoted to it in times of epidemics.

Friedrich has written a complete review of the published researches as to the persistence of cholera vibrios on food materials and has also carried on extensive experiments. It may be said that the cholera vibrio remains alive on foods more easily when they are protected from sunlight and kept in a cool moist place. Under such conditions Friedrich could recognize cholera vibrios on cherries after five days, on currants after seven days, on grapes after four days, on pumpkins after seven days, on cabbage after twenty days, and on the cut surface of pears after four days, on that of apples after seven days, on that of cucumbers after seven days, on that of pumpkins after fourteen days, in cocoa after seven days, in coffee after one hour, in Munich beer after two hours, in Pilsen beer after one hour, and in red wine after ten minutes. Rowland was able to demonstrate living vibrios in butter six days after inoculation. This shows that food materials which are not handled in a cleanly way, may very well act as the transmitters of the cholera vibrio.

The Transmission of the Cholera Vibrio by Insects.—This has been investigated experimentally by a number of authors. Living cholera vibrios have been found in flies one and a half hours after they had come in contact with cholera material. Flies have been caught in the ward in which cholera patients lay and it has been shown that the cholera vibrios were adherent to them. Further, flies were fed with cholera material, and it has been shown that their intestinal contents, examined with all possible precaution, still showed, after fourteen days, living cholera vibrios—which doubtless indicates an increase in the fly's intestine.

Resistance of the Cholera Vibrio to Chemical and Physical Influences.—Definite resistant bodies (spores) have not yet been found, but the cholera vibrio is able not only under specially favorable conditions to persist and multiply, but to keep up the struggle for existence under quite unfavorable conditions. They show themselves, however, very slightly resistant to measures immediately directed to their destruction. *Light:* Palermo proved that sunlight does not kill the cholera vibrio as long as the cultures are kept cool and Wesbrook confirmed this in so far as he showed that the destruction of the cholera vibrio takes place in sunshine only when air is admitted. According to Rieder the cholera vibrio dies under the influence of Röntgen rays in twenty or thirty minutes, while under the Finsen rays they die inside of a minute. *Desiccation:* In moist dust Germano was able to demonstrate the cholera vibrio for three months. In dry dust they died at once. According to Karlinsky the cholera vibrios remained alive on infected cloth for more than two hundred days as long as it was kept in a closed chest, but if the rags were dried before they were put into the chest the vibrios remained alive only thirty-six days. If cholera dejecta were used for such tests, instead of cultures, there appeared to be a far slighter power of resistance. On glass plates the cholera vibrios remained capable of development for as much as one hundred twenty days as long as the drying took place not gradually in the air but suddenly in a desiccator. *Heat:* The cholera vibrio is very sensitive to heat. The determinations of many authors agree that destruction is brought about by heating for ten minutes at 60° C.

Similarly, the powers of resistance toward chemical disinfectants is extraordinarily slight; thus, ½ per cent. carbolic acid kills them in ten minutes; 1 per cent. in five minutes; corrosive sublimate 1 to 1,000,000 in a few minutes, hydrochloric and sulphuric acid 1 to 10,000 in a few seconds, etc.

Pathogenicity and Virulence of the Cholera Vibrio.—The assertion was made by the opponents of Koch's theory that the cholera organism becomes non-virulent after passage through the human body and to produce an infection it must first undergo a sort of ripening in the soil. There are, however, means of proving that the cholera vibrio is virulent directly after its isolation from the dejecta of cholera patients. Koch made the gastric contents of guinea-pigs alkaline and introduced pure cultures of cholera. Others injected the cultures directly into the duodenum of the animal. In both ways a cholera-like intestinal disease could be produced. Similarly, fatal infections could be produced by subcutaneous and intraperitoneal injections into animals of pure cultures of cholera bacteria, which presented a condition of the intestine such as seen in cholera. Later, it proved possible to find animals which suffer from natural infections of pure cultures of the cholera; for example, Sabolotny showed that 50 per cent. of marmots die after feeding pure cultures of cholera, with lesions of the intestine corresponding with those of the human disease. Karlinsky and Metchnikoff were able to produce a fatal infection in sucking rabbits, dogs, or cats, by mixing cultures of the cholera vibrio with their milk.

Human beings, too, have sacrificed themselves for such experiments. Macnamara made an observation according to which 19 men drank water which contained cholera dejecta; 5 of them died of cholera. In the Hamburg Hygienic Institute, Oergel, who had been continually occupied in investigating cholera, died from a cholera infection at a time when there was no cholera in Hamburg. He had sucked up through a glass capillary tube a fluid rich in vibrios, and did not immediately disinfect his mouth. Several other laboratory cholera cases have been observed. In 1893, Pettenkofer and Emmerich drank a suspension of cholera vibrios in water. Both became ill with a violent diarrhœa lasting several days. It has been shown that, at least in some cases, the clinical picture of Asiatic cholera can be produced by simply swallowing cholera cultures which have been directly isolated from cholera dejecta without having undergone a ripening process of any kind. On the theory of Nägeli, which assumes the coöperation of two kinds of microörganisms in cholera, various investigators have made experiments. Among them Metchnikoff succeeded in finding a bacterium which greatly increased the pathogenic action of the cholera organism. Nencki has described bacteria which in themselves were non-virulent but which added greatly to the virulence of the cholera vibrio. This has no general significance because it is in the most intense cases of cholera that cholera vibrios are found in the intestine without associated bacteria.

Cholera Toxins.—Does the cholera vibrio set up a pure infection or produce, as Koch maintained from the beginning, a toxin? Gruber and other investigators held to the idea that the cholera vibrio acted as a purely infectious agent, and produced no toxins. R. Pfeiffer, however, showed that animals would die after inoculation with killed cholera vibrios. He filtered actively poisonous cholera cultures and showed that the bacterium free filtrate was not poisonous. From this he concluded that the cholera poison adheres

closely to the bodies of the vibrios but was not excreted by them, a view which many other investigators had taken. According to R. Pfeiffer, the symptoms are produced by the destruction of cholera vibrios in the body through which the poison is set free. In 1905 Kraus and Pribram obtained a toxin from cultures, which killed rabbits in a few minutes. This was only done with certain cultures, not with all, which explains Pfeiffer's earlier negative results. Kraus has obtained a specific antitoxin.

Immunity.—Gruber holds that in the case of cholera we must be dealing with an infection and not an intoxication, because it is not possible to immunize the animals against the poison but only against the infection. It has, however, appeared that, in connection with all bacteria which do not secrete a poison as the diphtheria bacillus does, but contain it in their bodies, like the typhoid bacillus, all efforts have failed which have aimed at rendering animals resistent to the poison in the way v. Behring has done in diphtheria. If one inoculates animals, *e. g.* guinea-pigs, rabbits, etc., repeatedly with the cholera vibrios they show themselves not much more resistant to larger amounts of killed cholera vibrios than normal animals. But the immunity becomes evident when one injects large masses of living cholera vibrios, which would surely kill normal animals, into these animals previously treated with cholera vibrios.

If cholera vibrios be injected into animals which have been treated with quantities of cholera vibrios which are not lethal, the cholera vibrios, as R. Pfeiffer has shown, are gradually destroyed in these specifically immune animals. Within a few minutes they are changed into minute particles or granules and killed. The further formation of poison is thereby inhibited. In animals which are not immune an active increase of the injected cholera vibrios may be observed.

Pfeiffer's Reaction.—R. Pfeiffer was further able to show that only cholera vibrios are influenced in this way in cholera immune animals and not other vibrios, not even those vibrios which cannot be distinguished morphologically and culturally from cholera vibrios. Through this discovery he assisted in a difficulty which was becoming awkward. In 1893, numerous vibrios occurred in the water of the Elbe, which resembled precisely the cholera vibrios. The question arose as to whether the inhabitants were to be warned against the use of the hydrant water. Such a measure would call forth a great outcry not only in Hamburg but in the whole civilized world which had dealings with that city. By means of Pfeiffer's method it was possible without difficulty to prove that the majority of the vibrios found in the water of the Elbe were not to be regarded as cholera vibrios. Pfeiffer was successful in making his specific immune reaction more practically useful by the discovery that it is sufficient to mix a small quantity of blood serum of cholera immune animals with the cholera vibrios in order to change them into granules and dissolve them even in the bodies of animals which had not been so treated before. This fragmentation occurs only in the animal body, not in a test-tube containing a mixture of cholera serum and cholera vibrios. Solution of the cholera vibrios could thus be produced only when some substance which is found in the normal animal body, that is some third factor found there, entered into play. Bordet was able to prove that Pfeiffer's reaction occurs also in the test-tube if a small quantity of fresh normal blood serum is added. One can thus observe Pfeifer's reaction outside the animal body. The establishment of this fact simplifies the technique still further.

Agglutination.—If cholera vibrios be mixed with cholera immune serum the cholera vibrios become non-motile and accumulate in little clumps. By this it was finally possible to exclude the group actions and to distinguish with certainty cholera vibrios from cholera-like organisms. For this purpose only those sera were used which caused distinct agglutination within a few minutes when diluted many thousand times.

The writer has made extended investigations to decide this point, in connection with cholera vibrios of wide origin. These have shown that the agglutination method is specific as long as bacteria are used which are not agglutinated by physiological salt solution or diluted normal serum. In other laboratories such universally good results have not been reached, but the impression is gained that old cholera cultures grown for a long time on artificial nutrient media are unsuited for such investigations. The unfavorable results are dependent upon the use of unsuitable culture media or upon some injurious influences. These new methods enable us to distinguish rapidly and with certainty the cholera-like vibrios obtained by means of the peptone preliminary culture from the true cholera vibrio. It is, in addition, even possible to test the blood serum of persons suspected of an infection with cholera as to whether it shows the specific cholera immune bodies. This, under certain circumstances, has been very serviceable in suspected cases.

Cholera Antitoxin and Vaccination.—After all efforts to produce an effective specific antitoxin for cholera had failed, cholera cultures have been injected for prophylactic purposes, analogous to Pasteur's vaccination, into persons who were especially exposed to infection. These injections were made first with attenuated or killed cultures and later with more virulent ones. Ferran is credited with having first made use of the method in cholera. It was then applied in a systematic way by Haffkine in India, with in part favorable results. By the inoculation of virulent cholera one may, according to the results of Pfeiffer and Kolle, produce an effect which may be recognized even after a year by the presence of the immune substances in the body of human beings and animals thus treated. Work is in progress to determine whether an effective protection may be reached by administering the products of metabolism of the cholera vibrio, without the vibrios themselves. The success of Kraus in obtaining a specific cholera toxin and antitoxin is of special interest in regard to the possibility of as satisfactory results as have been obtained in diphtheria.

Pathological Anatomy.—Bodies in the algid stage present a dusky gray-blue color. The lips, eyelids, and feet are often blackish-blue; the countenance is pale and sunken; the eyes are half open. The skin, loose and wrinkled, can easily be lifted. The abdomen is generally contracted and of a pasty consistence. Rigor mortis is marked. The fingers are often tightly bent and postmortem twitchings are frequent. As a rule nothing is seen of the exanthems observed *intra vitam*.

The subcutaneous tissue is dry; the musculature shows no striking change, nor is any characteristic alteration to be found in the central nervous system, except for the occasional congestion. The lungs frequently show lobar pneumonia, which may be observed from the third day of the disease, pulmonary œdema, and hemorrhages into the tissues. The mucosa of the air passages is often reddened and filled with mucous material. Hemorrhages of the size of lentils are often found in the pleura and over the epicardium. In the second and third weeks of the disease fresh hemorrhages are less fre-

quently found. The heart muscle in many cases shows considerable degeneration with slight cloudy swelling. The condition found in the peritoneum and in the intestinal tract is most characteristic. In a person dying in the attack, the small intestine presents a rose-red color, with great injection of the vessels and a ropy coating. The extent to which the intestinal loops are filled varies. Empty convolutions alternate with those which are distended and whose opaque white contents shimmer through. Agonal intussusceptions of the small intestines are also observed. The intestinal contents are usually like rice water but sometimes colored with bile or bloody, though at times simply diarrhœal.

The intestinal mucosa is sometimes of normal color, but as a rule is reddened and œdematous. But often, as for example in the later stages, in consequence of diphtheritic or necrotic processes, it is blackish-red with ecchymoses. The mucosa is, as a rule, deprived of its epithelium throughout considerable portions. The solitary nodules are swollen and show generally small hemorrhages in the centre. These changes are especially definite in the small intestine, particularly in the lower ileum, but they occur sometimes in the colon. The desquamation of the intestinal epithelium was regarded for a time as the expression of postmortem maceration, but according to E. Fränkel it is a vital process—the effect of the specific activity of the cholera vibrio.

Koch determined that the vibrios penetrate into the tubular glands of the intestinal mucosa and there produce an extreme irritation. Often the vibrios were found behind the epithelium of the gland. On the surface of the villi they are to be found in great numbers. With bloody infiltration of the mucosa, the bacteria are found in the deeper layers, in places even penetrating the musculature of the intestine. The chief seat of the invasion is in the lower ileum, where the most intense anatomical alterations are found. In the diphtheritic processes the mucosa of the intestine exhibited a deep necrosis with serous infiltration and swelling of the submucosa and muscularis. In the beginning of the diphtheritic process extensive hemorrhagic infarction of the villi occurs.

The stomach seldom shows characteristic alterations. At times there are necroses of the mucosa, and in these areas the cholera vibrios may be found.

The kidneys are intensely affected even as early as from four to nine hours after the onset. Macroscopically at that stage no alteration is found, except the opacity of the labyrinthine portion of the kidney; but microscopically, extraordinary swelling of the epithelium of the convoluted tubules may be observed. The portion of the cell body turned toward the lumen presents a sieve-like perforated appearance. The contours of adjacent cells are lost. The nuclei are seldom altered, as a rule only the cell protoplasm. Later there is a complete dissolution of the cells. From the second to the fourth days of the disease the kidneys show great congestion, so that the cut surface appears dark grayish-red, and in the border zone shows a dull-red color. Microscopically the glomeruli and intertubular capillaries are filled, and in the secreting parenchyma the plasmolysis is much further advanced. After the third week the regeneration of secretory renal epithelium begins.

The bladder is strongly contracted and contains only a little turbid urine loaded with hyaline and finely granular casts. From the third day on, one finds as a rule larger amounts of clear urine. The mucosa often shows minute hemorrhages.

The spleen is as a rule but little altered, although multiple hemorrhages of lentil to hazelnut size may be found in it. In the liver, beside slightly cloudy swelling of the parenchyma, there are seldom any changes. During the first days of the disease the gall-bladder contains a very little dark thick bile. Subsequently the bile is more liquid and clearer.

In the long bones the fatty marrow becomes gelatinous and of raspberry color. Occasionally focal or diffuse hemorrhages are found.

The blood, spleen, kidneys, and liver are as a rule free from bacteria. In the lungs foreign microöganisms occur. Rekowski reports, however, that in 14 cholera autopsies he found the cholera vibrios in the liver, kidneys, and heart.

Incubation.—At the beginning of a cholera epidemic one observes, beside the extraordinarily rapidly fatal cases of the disease, all gradations down to scarcely recognizable diarrhœa. These latter occur much more frequently than had been generally supposed. Cases also occur in which no symptoms whatever appear and only the discovery of the living cholera vibrios in the dejecta shows the existence of the infection. Many observations show that, following an indiscretion in diet, or emotional disturbances, rapid and unexpectedly severe choleraic symptoms may appear. It is clear from this that no unanimous results can be reached as to the incubation time. Based in results from individuals who came from cholera-free places to infected localities, it has been determined that the disease appears, as a rule, two and a half to five days after their arrival. The individuals who drank cholera vibrios sickened, at the earliest, twelve hours afterward. In epidemics the disease frequently appears twenty-four hours after the opportunity for infection. On the other hand the incubation period may last from eight to fourteen days. As a rule the incubation period lasts from two to three days, but if one reckons the slight prodromal diarrhœas, it must be regarded as shorter.

Symptoms.—At present five forms of cholera are distinguished:

1. **Cholera Infection Without Definite Symptoms.**—Here living cholera vibrios are found in the liquid, semi-solid, or even solid stools of completely healthy persons who show no symptoms, or scarcely noticeable symptoms, of intestinal disturbance. Under unfavorable conditions this may pass on into the more severe forms, but in many cases the cholera vibrios soon disappear from the stools without definite disease having existed.

2. **Cholera Diarrhœa.**—In this more or less frequently yellowish stools, colic, flatulence, coated tongue, thirst, and a feeling of pressure in the region of the stomach are observed. The condition may be recovered from in a few days or it may become more severe.

3. **Cholerine.**—This is characterized by rice-water stools, vomiting and general disturbances. Forms 2 and 3 were previously described together as the first stage of cholera and spoken of as prodromal diarrhœa.

4. **Pronounced Cholera.**—This was previouly called the second stage of cholera.

5. **Stadium Comatosum.**—The patient shows extreme intoxication with cessation and decrease of the stools and vomiting, sometimes with fever, but oftener with subnormal temperature; he becomes somnolent, delirious and comatose. Frequently anuria appears, which is an unfavorable sign, as is also a subnormal temperature. The forms with fever often result favorably. The cholera diarrhœa may sometimes pass directly into the stadium coma-

tosum without there having been at any time a typical attack of cholera. Since the cholera vibrios may be demonstrated as long as the third or fourth week of the disease, it is not impossible that the stadium comatosum is to be regarded as a sort of chronic cholera.

Since the mildest cases differ not at all from an ordinary diarrhœa, we need only concern ourselves with a typical pronounced case of the disease. This presents the following symptoms: In the first part of the so-called prodromal stages thin, fluid masses of normal color are discharged without pain or straining, although there are some colicky pains in the abdomen. At times loss of appetite, slight feeling of nausea, dulness and lassitude are present. The hands and feet may be cold. These symptoms may disappear in one or two days or the condition may become suddenly worse and the second stage develop (the true cholera attack), with unusually thin fluid stools, rapidly following one another without any tenesmus. In the beginning the discharges are bile-stained, but later they become colorless and have a watery appearance, rendered turbid by grayish-white flecks—the so-called rice-water stools.

Simultaneously vomiting sets in. At first everything the stomach contains is ejected; then the vomitus assumes the character of the rice-water stools. Often there is singultus. The appearance of the patient changes rapidly; the skin becomes lax and wrinkled and when folds are pulled up they disappear slowly. The nose becomes thin and pointed, the eyes sink deep into their orbits, and the cheek bones stand out prominently. This is the *facies cholerica*. The heart impulse, the heart sounds, and the pulse, become weaker; the nose, ears, and extremities feel cool; the skin assumes a dark gray color; grayish-blue rings appear around the eyes; the lips become bluish, as do also the hands and feet, especially around the nails. The secretion of urine gradually ceases; torturing, unquenchable thirst ensues; cramps appear in the calves, in the thigh muscles and in the muscles of the arms and abdomen. The reflexes are greatly diminished; the pupils react only slowly. The voice becomes hoarse and toneless. A sensation of suffocation arises. The patient is completely exhausted, complains of faintness and palpitation of the heart as well as confusion, anxiety, and a feeling of heat, although the surface temperature is subnormal, while in the rectum it may be 104° F. The greater the difference between these two temperatures, the more unfavorable the prognosis. Consciousness remains complete but the patient sometimes becomes apathetic. In the most severe cases the disease passes on into the third stage (stadium algidum) which in the great majority leads to death. This stage is characterized by almost complete cessation of circulation. The action of the heart is weak and irregular; the first sound is impure, the second often inaudible: the radial pulse almost impalpable. If a well-filled vein be cut, dark and thick blood flows which does not become lighter in the air. In the worst cases no blood flows at all, even if arteries are cut. The breathing is labored; the skin is moist and cold, often covered with sticky perspiration. The skin is lead-gray; the fingers, toes, and ears, dark violet; the discharges decrease gradually; the patient is completely voiceless; dark spots appear on the conjunctivæ, and the cornea becomes opaque. Friction murmurs appear in the pericardium and pleura as a result of lack of moisture. Consciousness is still present but dulled. Violent thirst, precordial distress, and a feeling of depression persist. This death-like condition gradually passes into real death, sometimes only a few hours after

the beginning but often not until the second day. Recovery after this stage seldom occurs.

The Stage of Recovery (Stadium Restitutionis or Reactionis).—The vomiting ceases, the stools become less frequent, of greater consistency and gradually assume a bile-stained appearance. The symptoms described gradually disappear. In less severe cases complete health may be recovered in a few days; in others convalescence is long and the heart action remains weak and variable. The urine contains large amounts of albumin. Sometimes febrile periods occur—the reaction fever, which lasts for one or more days with rapid pulse, dull heart sounds, headache, and even delirium and somnolence. While exanthems do not appear in the height of the attack, the most various changes in the skin may be observed in the stage of restitution. These may be bluish-red spots or swollen red flecks forming a rose-color rash and larger erythema-like patches of red color and of various forms which may be spoken of as *erythema annulare*. Sometimes also nodules are seen, the *roseola papulosa* or urticarial wheals may form. Finally there may be extensive reddening and swelling which resembles erysipelas. Small hemorrhages, larger vibices and sugillations may appear or vesicular eruptions and wheals. These exanthems occur most frequently on the extremities. In convalescence there is a tendency to the formation of furuncles and in some cases even phlegmonous inflammations.

Cholera was previously considered as a general disease chiefly on account of the exanthems observed in its course but is now regarded as a local infection of the intestinal tract with a consequent intoxication. Symptoms have been observed also in diseases which begin with a great loss of fluid, which have the greatest similarity to those of the severe types of cholera. Not only is the general appearance of the patient similar but also the muscular cramps, inspissation of the blood, etc. By administration of water in such cases it is generally possible to overcome these symptoms. According to some the majority of the symptoms of cholera may be explained by a simple loss of water which results from the action of the toxin of the cholera vibrio.

Against this intoxication theory, the objection is that the most severe symptoms appear at a time when the intestinal mucosa is so altered as to be incapable of absorbing any poison, but before the destruction of the mucosa sufficient poison may be absorbed to explain these phenomena. There was a tendency to explain the exanthems as due to circulatory disturbance. This might be true in the case of the bluish patches, and gangrenous processes, but most of the other exanthems are probably the direct result of the action of the toxin. Until recently decisive observations were lacking, because one could not apply experimentally such toxins as might be here concerned. But as the introduction of the smallest quantities of pollen toxin causes in a short time the most varied exanthems, which in many cases are exactly similar to those seen in the cholera, the explanation of the cholera exanthem as the result of a direct action of the toxin seems fortified. The appearance of the exanthem is generally thought to be an unfavorable symptom.

Complications and Sequelæ.—In many patients complications appear which are a more or less direct result of the disturbances caused by cholera intoxication. These have been explained as due to decreased resistance to injurious influences. Besides the nephritis, the exanthems, the diptheritic inflammations, and the hemorrhages, which occur in all mucosæ, pneumonia

and infarcts in the lung, spleen, kidneys, and other organs may also occur. In rare cases pleurisy, peritonitis, meningitis, abscess formation, bronchial catarrh, catarrhal cystitis, icterus, and venous thrombosis occur. In many patients anæmia, emaciation, and general debility, especially in the digestive functions, follow. In certain cases this may amount to marasmus, and in rare cases mental weakness or even insanity, generally of a melancholic character, may appear. In habitual drinkers, cholera may occasion an attack of delirium tremens.

The most frequent and characteristic sequel is the "*cholera typhoid*," which occurs in about one-quarter of all severe cases in the second half of the first week. General debility and exhaustion appear with a special limitation of the psychical functions. Apathy, sleepiness, headache, serious disturbances of consciousness, delirium, a soporous condition, even amounting to deep coma, occur. Cramps in different muscles are frequent; generalized convulsions are less common. The tongue and lips are dry and cracked, often with blackish sordes. Rales are to be heard throughout the lungs. There may be considerable elevation of temperature and frequently a dicrotic pulse as well as quickened breathing. An attempt has been made recently to explain the "cholera typhoid" chiefly as a result of poisoning with cholera toxin. But undoubtedly the action of foreign bacteria is important. The phenomena may be explained under certain circumstances, according to Liebermeister as chiefly the result of changes which the brain has suffered in an attack of cholera. In other cases uræmia forms the basis.

Treatment.—Until good results are obtained from the specific antitoxin we are still dependent on expectant or symptomatic treatment. In cholera without symptoms, *i. e.*, in the mild diarrhœas, it is necessary to provide a regular mode of life, and prevent excess of every kind, especially in eating and drinking. The use of *opium* has not always proven rational. After a transient cessation of the diarrhœa severe disturbances often appear. Koch used opium to quiet the intestines of the animals experimented on and in this way gave the cholera vibrio an opportunity for multiplying. With the hypodermic use of morphia, a favorable influence on the circulation was in many cases brought about; the cyanotic color disappeared and the pulse was improved.

Specific antiseptic materials which might be expected to inhibit the growth of the cholera vibrios in the stomach and intestines have been without value. We have fallen back on materials which cause the organisms to be forced out of the intestinal canal. Castor oil and especially calomel have been used. According to Rumpff, it is best to give 0.03 to 0.05 gm. (gr. $\frac{1}{2}$ to $\frac{3}{4}$) of calomel every two hours for one or two days. In this way the adult takes a maximum of 0.6 to 1.0 gm. (gr. 9 to 15). For children the dose is to be correspondingly diminished. If the pulse of the patient become rapid and small the hypodermic injections of morphia prove helpful.

In well marked cases the vomiting interferes considerably with the treatment. Sometimes this may be temporarily stopped by the administration of small pieces of ice. In other cases a quieting of the stomach must be attempted by narcotics. Injections of morphia of 0.005 gm. (gr. $\frac{1}{12}$) and more are recommended for this. The vomiting and cramps may be relieved and also the excitement and the subjective disturbances. Hot baths affect some patients favorably, but they must be interrupted if attacks of fainting or collapse appear. In individual cases it was observed that the cholera

exanthems developed as an immediate consequence of the hot baths; in other cases the blue-gray color of the skin disappeared, as well as the cramps; the pulse improved and convalescence set in. In many cases it is necessary to give several baths.

When the pulse becomes small and the heart sounds weak, camphor oil should be given hypodermically. Fluid can be given by intravenous or subcutaneous injection of salt solution, but it is yet undecided as to which of these methods is preferable. Sometimes after the intravenous injection of a liter of fluid at about 40° C. the pulse improves, the respirations become deeper, the somnolence disappears, and the skin assumes a reddish color. But the course is not so favorable in all cases and there may be no reaction whatever. Occasionally after several injections and as much as six liters of salt solution have been given, a permanent good result is attained. Of such apparently rescued patients some die of coma. Cantani, who recommended an enema of tannin, prefers subcutaneous injection to the intravenous, because the mixture with the blood takes place more slowly and thoroughly. In the stadium comatosum, baths up to 35° C. with subsequent packs in woolen blankets, as well as sweat baths, after abundant administration of milk and water, are recommended but the results are seldom favorable.

Measures for Combating the Epidemic.—Before everything, it is important to recognize at once the first case of the disease and to take measures to prevent its transmission and spread. It may be regarded as the duty of every physician to see that in every suspicious case there is at once an expert examination of the dejecta for the cholera vibrio. Until the examination is completed the patient is to be treated as if he really had cholera.

As soon as Asiatic cholera is recognized all efforts must be turned toward the discovery of the source of infection. It is especially important that the board of health be immediately notified. In most countries the measures which must be carried out on the appearance of cholera are defined by law. Procedures were agreed upon by the Dresden convention of 1893, as well as by the International Conference at Paris in 1894, by which an effort was made to prevent cholera from leaving the country in which it originated and also to prevent its traveling from one European country to another. If these measures are carried out in such a systematic way as they were in the years 1893–94, and especially 1905, in Germany, we shall not have much more to fear from Asiatic cholera in Europe and America, and it might then be considered as the disease of the nineteenth century. Unfortunately many countries are not so well prepared for the struggle as Germany, and one can not everywhere depend on finding the necessary coöperation. In 1894, cholera, although it was introduced into hundreds of German localities, could be regarded as completely extinguished in that country. In adjacent countries, however, it then raged in a most destructive way. In 1905 it was again introduced into more than 100 German localities but was extinguished in all within a few months. This brilliant success in Germany was due entirely to Koch's logical plan of fighting the disease. He stated that "however simple or complicated one may regard cholera, there is always a chain of circumstances which is sometimes short and sometimes very long. As soon as we succeed in breaking a single link in this chain, the chain whether long or short must break. That link of the chain which we know most exactly and against which we can act most successfully is the cholera vibrio. Of the other necessary causes we still know too little to use them

practically in the struggle against cholera. As soon as we know them we will naturally use them also."

The cholera germ is present in a condition capable of producing infection in the intestinal contents of persons suffering from cholera; it may also be found after recovery from the disease, and may also occur in individuals exposed to infection although they show no symptoms of the disease. In order to start a new infection the cholera germ must, without having previously become dry, gain entrance into the digestive tract of a susceptible individual. It is not spread through the air. Direct transmission is more frequent the more unclean the surroundings of the patients. With sanitary surroundings such transmission may be prevented. Soiled clothes are especially to be considered, as well as the infected persons themselves, in the transmission of the germ. The most usual medium for transportation is water, on the one hand because it preserves the germ well, and on the other hand because it is more readily defiled by cholera dejecta than any other one food material. Besides, water most easily carries the cholera germ uninjured through the stomach.

With those who recognize the correctness of this state of affairs there can exist no important differences of opinion as to the means to be taken to protect against cholera. Such measures, however, involve in part serious injuries to property, not only for the individual and communities but also for whole provinces. One must assure oneself in connection with each measure that the good to be obtained is commensurate with the damage produced. The responsibility for the ordering of measures which exceed certain limits should be left to the higher authorities. It has always been the tendency, especially among the laity, to proceed to the extravagant use of disinfectants even in places which the cholera infection could never reach. The safest guard against cholera is to be sought in the abundant provision of cities and localities with unquestionably good water, as well as careful removal of fæcal material and garbage. In communities whose water supply is perfectly good one may without great difficulty prevent the introduction of the cholera germ.

As to the conditions of life, much can be done in a preventive way. Where people live crowded together in a dark dwelling, the disease finds its most favorable soil and forms foci and spreads uncontrollably. On the basis of such experiences it has been called the disease of the proletariat. Less is to be expected of limitations of intercourse. The leading authorities have not allowed themselves to err in the idea that intercourse should remain perfectly free. On the basis of experience in Germany, transportation of freight may be allowed to go on freely and the transportation of people may be limited merely to their undergoing medical supervision. Even persons coming from an infected region may enjoy unlimited freedom as long as some supervision is kept over them. In the case of homeless people, tramps, etc., who have been shown to be especially prone to cholera infection, a more thorough control is justified. This is true also of immigrants who come from infected regions. Further, the crews of river boats are to be carefully watched in time of cholera infection. The value of a quarantine for foodstuffs is not commensurate with the injury that arises from such a measure. Each person, however, should make a rule to eat nothing uncooked that does not come from a thoroughly trustworthy source.

For ships, instead of quarantine, a medical review together with rational methods of disinfection is suitable. Suspicious persons only should be kept

under observation, and these for not more than five days. In view of such measures we may finally throw aside completely the system of hushing up cholera epidemics formerly so much adopted.

In Germany the central boards of health have sent especially trained physicians and nurses to infected places. This plan has been particularly successful. The patients must be at once isolated. Where the hospitals are insufficient one may conscientiously use the schools for the accommodation of the sick. The disinfection of dwellings may be limited to the excreta and objects that have been soiled. Infected, overfilled, and miserable dwellings, wretched hovels, etc., should be cleaned out on the appearance of cholera. Such prophylactic measures are especially important in ships. Special care must be employed in preventing the infection of drinking and wash water.

The German Federal Council adopted rules in 1894, which everyone should keep for reference who has to do with the struggle against cholera. In these directions the plans for disinfection are set down in detail. The proposal is there made also, that in cholera infected places a health commission should at once be organized, which might support the municipal authorities in the carrying out of the efforts against the disease. The necessary procedures for disinfection are described, and further arrangements are given for the reporting of cases.

A detailed repetition is not possible here, but we repeat the directions which refer to the bacteriological determination of the cholera vibrio and to disinfection.

Procuring Material—From the Living Subject.—About 50 cc. of the dejecta are taken without the addition of any disinfectant. A number of cover-slips are to be smeared with the dejecta, preferably with a particle of mucus, for microscopic investigation. When possible several agar cultures are to be made on the spot. Linen freshly soiled with dejecta is to be treated in the same way as the dejecta themselves.

From the Cadaver.—The peritoneal cavity is opened and three loops of intestine, 15 cm. long, are ligated at each end and taken out; one is from the middle part of the ileum, one about 2 meters above the ileocæcal valve, and one immediately above it. The last-mentioned is the most important. Thick walled bottles with boiled corks may be used for sending this material. These bottles must be freshly boiled and must not come into contact with disinfectants. The microscopic examination is made with smear preparations which are to be stained with diluted carbol-fuchsin (1 to 9). Hanging drops are prepared with peptone solution and these are to be examined immediately, and after half an hour's incubation at 37° C.

Two series of gelatine plates are prepared, of which the original plates are to be smeared with a small fleck of mucus or with a loop full of the material. The gelatine plates are best incubated at 22° C. After eighteen hours the examination may begin with the use of a cover-glass preparation. The agar is poured out into Petri plates and dried for a half hour. Then the surfaces of the plates are successively smeared with a fleck of mucus. The agar plates may be examined after remaining from eight to twelve hours at 37° C.

Peptone Preliminary Culture.—Reagent glasses with 10 cc. of peptone solution are infected and, after remaining from three to twelve hours at 37° C., examined microscopically. If cholera-like vibrios are found on the surface, agar and gelatine plates are made from this culture. Further small vessels with 50 cc. peptone solution and 1 cc. material are prepared and,

after being incubated at 37° C. for from three to twelve hours, are examined. From the plates suspected colonies are transplanted on agar. After the development of these the agglutination test is carried out. Water suspected of being infected is made into a 1 per cent. peptone solution by the addition of concentrated peptone solution in quantities of 50 cc. to 1 liter of water. After remaining from eight to twelve hours at 37° C. this is examined in the same way as the peptone preliminary culture. In 1905 the writer added cholera serum directly to a fleck of mucus or to a drop of the dejecta and thereby was able at once to declare cases as not being cholera, although the dejecta contained cholera-like vibrios and the patients had suspicious symptoms. The negative results were confirmed later by other methods.

With the first case of the disease in a locality all methods of investigation described must be made use of. After the presence of the cholera vibrios is established, the investigations may be considerably curtailed.

Interpretation of the Results.—The diagnosis is regarded as certain when all the morphological and cultural characteristics are met with and the agglutination test as well as Pfeiffer's reaction are positive. Convalescents are to be regarded as no more infectious when the examination has proven negative on three days, each separated by one day.

Disinfection in Cholera.—The following are to be considered as disinfectants, cresol water (2½ per cent.), carbolic acid solution (3 per cent.) chloride of lime (1 to 50), milk of lime 1 to 5, formaldehyde, and disinfection by steam and in suitable cases by boiling. The dejecta are mixed with equal quantities of the above-mentioned fluids and after two hours the disinfection may be regarded as complete. For the disinfection of soiled clothes, cresol water is recommended. For the disinfection of dirty water, chloride of lime and milk of lime are useful; for closets, cresol water and milk of lime; for the contents of privy pits, chloride of lime and milk of lime.

The disinfection of the hands and other parts of the body may be accomplished by cresol water and carbolic acid solution. Bed linen and underclothes, washable pieces of clothing, etc., are to be boiled or placed in carbolic acid solution for a period of two hours. Pieces of clothing which cannot be washed, mattrasses, carpets, etc., are to be disinfected by steam. The surroundings of the patient are to be washed with cloths soaked in cresol water or carbolic acid solution. It is necessary to disinfect the place where the patient or corpse lies and the neighborhood for a distance of about 2 meters. Formaldehyde disinfection comes into use in cholera only for surfaces, as the walls of a room. Leather, wood and metal structures are washed thoroughly with carbolic acid solution or cresol water. Furs are washed with the same solution. Earth, plaster, sinks, etc., are disinfected with diluted cresol water or milk of lime.

The bodies are wrapped in cloths soaked with cresol water. The floors of the coffins are covered with sawdust, peat dust, or other absorbent material.

CHAPTER XXVII.

YELLOW FEVER.

By JAMES CARROLL, M.D.

Synonyms.—Yellow jack, bilious remittent yellow fever, hæmagastric pestilence, black vomit, Gibraltar fever, Barcelona fever, fièvre jaune, Gelbes Fieber, el vomito, fiebre amarilla, typhus icterodes, pestis Americana, febris maligna biliosa, etc.

Definition.—An acute, specific, infectious, but non-contagious disease, characterized by fever occurring occasionally in one, but generally in two, paroxysms; the first of these is of short duration and followed by a brief remission or intermission which is succeeded in turn by secondary fever, accompanied by albuminuria, jaundice, passive hemorrhages from the mucous membranes, and, in severe cases, black vomit.

History.—As far as can be gathered from the history of the New World the central portion of the American continent has always been the endemic home of this disease. The earliest authentic accounts locate it in the middle of the seventeenth century in the Antilles, whence it was carried to adjacent ports by the early Spanish navigators who also conveyed it to more distant localities. The disease is largely one of seaport towns and maritime districts in tropical and subtropical climates. Hence on account of her geographical situation, her extensive coast-line, and her large commercial interests, the United States has suffered more from yellow fever than any other country. Her medical history teems with accounts of epidemics of yellow fever and bilious remittent fever, and descriptions of the latter justify us in considering them, certainly the majority, to have been yellow fever. Certain places or localities have long been regarded as permanent endemic foci of yellow fever; among these may be mentioned Vera Cruz, Havana, Rio de Janeiro, and the west coast of Africa. The disease has become endemic only in places situated within the tropics; from these it may be carried to subtropical regions, where its ravages continue during the greater part of the year, until the inhabitants have become immune, or its progress has been arrested by the occurrence of frost. In the temperate zone it may be introduced and fail to spread, or, if it be accompanied by the proper mosquito, it may destroy thousands of lives within a few months. Here, also, the appearance of severe frosts puts an end to the outbreak. That the infection may be carried long distances on water has been shown by the occurrence of outbreaks at Barcelona and other Spanish ports during their intercourse with the West Indies, and by the losses suffered by the British in the transportation of their troops between the West Indies and the west coast of Africa or the northern part of this continent. It has seemed remarkable that, notwithstanding her constant intercourse with infected ports and the frequent occurrence of the disease upon her vessels, Great Britain has never experienced a widespread epidemic of yellow fever; but we know now that her climate is not favorable to the propagation of the carrying agent of the disease—a mosquito of the genus

Stegomyia. A century ago the British troops and foreign inhabitants in Jamaica were from time to time decimated by this pestilence, and the island was designated the white man's grave. It was soon learned from experience that people could escape the infection by removing to mountainous districts during the warm season, and by acting upon this knowledge they have eradicated yellow fever from the island. This is explained in the following way. The infection exists only in man and in the mosquito, which has become a domesticated insect. During the season of the year when epidemics were known to prevail, non-immune persons were advised to leave the city and reside in the hills surrounding it. The native negroes who remained were wholly or partially immune. When cases of the disease were received by importation during the warm season, there were few or no susceptible persons at hand through whom extension could take place; consequently when the non-immune residents returned in the winter season the mosquitoes had become inactive and the danger was removed.

It was observed long ago by the British surgeons in the West Indies that the incidence of cases of yellow fever was proportionately much greater among men who slept upon the ground floor of the barracks than among those quartered in the second story. William Ferguson,[1] a surgeon at Sierra Leone, reported in 1839 that an interval of three or four weeks always elapsed between the landing of the first cases and the appearance of the epidemic following. Carter[2] confirmed these important observations sixty years later in the United States and fortified them with data.

It was shown in Baltimore, more than a century ago, that yellow fever was non-contagious, for hundreds of cases were treated in the city proper and no extension took place from them.[3] Yet it was just as clearly shown that in the majority of instances the persons who became infected had visited certain wharves or their localities after dark. It was also remarked that, during the epidemic, the city was badly infested with mosquitoes, while ordinarily it had been remarkably free from them. These observations are of the greatest historical interest because of their bearing upon the mosquito theory, which at that time had not been demonstrated, but by means of which at the present day every known fact in connection with the etiology of the disease can be explained.

In 1878, yellow fever was successfully controlled in Mobile, Ala., as long as quarantine of the patients and sulphur fumigation were practiced; but upon the discontinuance of the former an epidemic took place. On the Island of Cuba, at the City of Santiago, yellow fever disappeared in 1899, because during the American occupation all suspicious cases of fever were removed at once to an island nearly one mile across the bay. The mosquitoes that were infected on this island could not become a source of danger to the city, because only immune persons were permitted to accompany the patients who were taken there, and though some of the latter suffered from yellow fever after recovering from malaria, the inhabitants of the city escaped any further infection.

Within the past five years, Havana, one of the chief endemic foci of yellow fever, has been entirely freed from the disease by the systematic institution and maintenance of measures based upon the proved theory of its con-

[1] *London Medical Gazette*, August 31, 1839, p. 843.
[2] *The New Orleans Medical and Surgical Journal*, May, 1900.
[3] *Medical Repository*, New York, 1820, vol. xx, 261.

veyance by the mosquito. In 1903 a rather extensive epidemic prevailed in Mexico and the disease invaded the United States, with the result that over 1,000 cases appeared in the state of Texas. After the usual quarantine measures had been tried it was found necessary to adopt the means that had proved so successful in Havana, and in this way a widespread epidemic was, in all probability, averted.

We have to record another severe epidemic in New Orleans in 1905, with the unusual occurrence of the enforcement of quarantine regulations by the city of Havana against a port of the United States on account of yellow fever. Indeed there may be good ground for the assertion that in this instance Havana received the infection from New Orleans, which was much more exposed through constant intercourse with Central American ports and became the seat of a serious invasion which extended to other localities, even beyond the limits of the state of Louisiana. This epidemic produced over 8,000 recognized cases and caused more than 900 deaths. It brought about an awakening in the minds of the officials and of the intelligent public to the serious nature of the problem of the protection of the city, and through it of the state and the country, from yellow fever, and to the necessity for more stringent regulations governing the early isolation and prompt recognition of cases of this disease. It was realized that disaster must still continue to follow upon the former lax measures and practice of concealment of cases, and the officials and local physicians now appreciate the tremendous responsibility that rests upon them.

The presence of the disease was not declared until it had secured a firm foothold, and it then required the united efforts of the officials of the United States Marine-Hospital Service and the local physicians to bring the condition under control. A campaign of education of the people was undertaken by the officials, clergymen, physicians and ladies of the city, upon the basis of the mosquito doctrine of the transmission of yellow fever, in order to explain to them the methods that were adopted in the attempts to exterminate the mosquito and to protect patients and others against it. As the result of these combined efforts the disease was completely eradicated before the occurrence of frosts. This was something that had never been accomplished before, and it had become traditional in that latitude that suppression of an epidemic of yellow fever in a large city could never be looked for until the appearance of heavy frosts. In the season referred to, New Orleans contained a larger non-immune population than ever before, and the disease had been permitted to become firmly established by the month of July; nevertheless the situation was brought under complete control at a time when, according to all precedents, it should have been absolutely unmanageable.

In the same year a small outbreak occurred at Belize, British Honduras, and a timely inspection by Professor Rupert Boyce, of the Liverpool School of Tropical Medicine, brought out the interesting fact that the disease probably existed there as early as January but was not declared until May. The prompt infection of 8 men in two of the hotels of Belize, where they arrived on the 11th of May, shows the existence there, at that time, of infected mosquitoes. These men were non-immunes from a steamship stranded on the coast, and they were taken ill at intervals of a day or two until the 29th. Dr. Boyce recognized the important fact that in Belize, as well as at New Orleans and other places, the first cases escaped recognition

and the disease was permitted to become firmly established before its presence was declared.[1]

It is quite possible that during the same year the disease was also imported into Havana from New Orleans. Havana became and still remains infected, though the authorities keep the situation well in hand, and with their usual vigilance there is no reason to fear an epidemic.

It is to be hoped that before long success will attend measures inaugurated in Mexico, Brazil, British Honduras, Panama, and nearby harboring places of the disease, and that the continent will become free of the fatal pest that has been its greatest terror for centuries. This may best be effected through international agreement and coöperation on the part of the countries directly concerned, and for such measures the situation is now ripe. Space will not permit a consideration of the numerous epidemics that have occurred in the United States. Nearly every one of her seaports has been invaded and her losses have been enormous. Many of the inland towns along navigable water courses and railroads have also received the infection and been decimated by it. In Europe, at various times, this disease has visited Spain, Portugal, Italy, France, England, and Germany. In Spain alone the deaths recorded for eight epidemics between the years 1800 and 1821, inclusive, were no less than 130,000. Barcelona lost 20,000 persons from this disease in 1821.

According to the available records about 100,000 deaths from yellow fever have occurred in the United States since 1793. The cities to suffer the most have been New Orleans (40,000) and Philadelphia (10,000). As late as 1878 the mortality from yellow fever in the city of Memphis, Tenn., was more than 5,000 in a single epidemic. About 25,000 deaths are recorded for Rio de Janeiro, and nearly 36,000 for the city of Havana from the same cause.

Etiology.—Few diseases, with the exception of plague and cholera, have inspired the same horror and fear as yellow fever. Wherever it has raged commercial interests have been paralyzed, and cities, towns, and districts, have been depopulated. The early medical history of Philadelphia is one of a succession of epidemics, and here, as well as in other cities and countries affected, the best minds of the profession have devoted their attention to the subject of the etiology of the disease, in the hope of securing knowledge that would enable them to suppress or control its ravages and treat it with success.

From the time of Benjamin Rush the transmission of yellow fever through the atmosphere has been taught and believed by leaders in the profession; but such declarations were met with seeming proofs of its transmission by indirect contact, and by some it was held to be even directly contagious. Rush held that the infectious agent originated *de novo* from matter of a vegetable nature undergoing decay in the presence of water; but he finally abandoned this belief after years of controversy. English and Spanish physicians who had passed through large epidemics were about equally divided in opinion upon the subject, and this confusion continued for centuries. No matter to which side of the argument an authority might lean, facts and evidence were always forthcoming to show that his theory did not explain all the conditions to be encountered. For instance, persons who

[1] *Report to the Government of British Honduras upon the Outbreak of Yellow Fever in that Colony in* 1905, by Rupert Boyce, London, 1906.

secluded themselves during an epidemic frequently became infected, while on the other hand, many who were in constant attendance upon the sick in hospital escaped infection; and again, a single visit to the sick, and only one visit, was shown in many instances to be sufficient to insure an attack. The fact that certain buildings or localities, and vessels in particular, retained the infection during the warm season, or in tropical regions, and the constancy with which the infection appeared to cling to the vicinity of water, led to the belief, and with reason, that it resulted from fermentation, the most favorable conditions for which require the presence of heat and moisture. It was repeatedly observed that extensive epidemics were accompanied by conditions of high atmospheric temperature preceded or followed by heavy rains. The beginning of many epidemics could be traced to the presence of vessels recently arrived from the tropics, and as the holds of wooden vessels were nearly always in an offensive condition, the fermentation theory received strong support. After the discovery of bacteria as the cause of fermentation and putrefaction, as well as of disease, there seemed to be no longer any room for doubt. It was very difficult to explain why persons suffering with the disease often failed to communicate it to others after having been removed only short distances. For example, certain hospitals in the suburbs of infected cities which received a large number of cases of yellow fever, often failed to show a single secondary case, notwithstanding the fact that free intercourse with the patients was permitted and no precautions were taken.

Further it was shown, as in the case of the Leyden,[1] that persons who contracted yellow fever on shore might be treated at a sufficient distance from the shore, on board vessels, without danger of communicating the disease to other persons on the same vessel. On the other hand, it was also well known that vessels frequently became infected while lying at ports where the disease prevailed; and these facts were hard to reconcile.

Inexplicable mystery continued to surround the origin and dissemination of yellow fever until quite recently, and this mystery, with the dread inspired by the black vomit, often led to the abandonment of business, home, and friends, regardless of family ties or financial interests.

Special importance now attaches to the observation recorded by Dr. Drysdale[2] in Baltimore, in 1794. In writing to Benjamin Rush of Philadelphia, in that year, he said: "Locusts were not more numerous in the reign of Pharaoh than mosquitoes through the last few months; yet these insects were very rare only a few years past, when a far greater portion of Baltimore was a marsh." Dr. Rush himself wrote later that in 1797 and 1805, during the occurrence of epidemics of yellow fever in Philadelphia, "flies and mosquitoes were infinitely multiplied"; and that "mosquitoes abounded, as usual, in sickly seasons."[3] The statements also of Dr. John Vaughan,[4] of Wilmington, Delaware, that in 1802, the year of an epidemic, from July until frost the lower parts of the town were infested with myriads of mosquitoes, that within the memory of the oldest resident these insects had not been troublesome before, and that in August the season was tropical and rain

[1] *LaRoche on Yellow Fever*, Philadelphia, 1855, vol. ii, p. 509.

[2] Ninth letter of Dr. Drysdale to Dr. Benjamin Rush, *The Philadelphia Medical Museum*, 1805, vol. i, p. 26.

[3] *Medical Inquiries and Observations*, Benjamin Rush, M. D., Philadelphia, 1805, vol. lv, p. 77.

[4] *Medical Repository*, New York, 1803, vol. vi, p. 301.

abundant, show that the older physicians were close and accurate observers. Other and similar observations were made from time to time, until Nott,[1] of Mobile, Ala., in 1848, in a most remarkable paper, directly incriminated the mosquito, or some similar insect, as filling the requirements for a possible conveyer of yellow fever, and Dowell,[2] of Galveston, in 1876, also called attention to the fact that the mosquito is governed by the same natural laws as yellow fever. Finally, in 1881, Charles Finlay, of Havana, published the first paper in which the mosquito, solely, is accused of transmitting the disease. But before discussing this phase of the subject farther, it will be proper to mention first the work that has been done in the attempts to establish a bacterial origin for this disease.

The first announcement of the discovery of a bacterium as the cause of yellow fever was made by Domingos Freire, of Rio de Janeiro, who, in 1883, described his *Cryptococcus zanthogenicus* and claimed that it was the specific cause of the disease. He proceeded to vaccinate human beings with it and continued to do so for some years, concluding in the meantime that his inoculations conferred a marked degree of protection. Cultures of the same organism, when inoculated subcutaneously early in an attack, were believed to manifest a curative value.

Carmonary Valle of Mexico, Charles Finlay of Havana, and Gibier of Paris, followed after Freire, and each thought that he had discovered the specific bacterial cause of the disease; but subsequent investigations by Sternberg showed that they had been mistaken. Sternberg himself, after several years of painstaking work, reported a negative result, and but little more was done in this direction until Guiseppe Sanarelli announced in 1897, that he had found and cultivated the causative agent, and that by means of inoculations with it and with its filtered products, respectively, he had produced the characteristic lesions of the disease in lower animals and the clinical phenomena in men. He named the organism that he had found *Bacillus icteroides,* and reported that he had isolated it upon ordinary culture media from about 50 per cent. of the cases examined. Sternberg in his work had obtained a bacillus from about the same proportion of his cases by the use of the ordinary culture media, and he had found that it also proved to be quite pathogenic for the lower animals. Because of his inability to establish its identity by the methods then available, he named it Bacillus X, and caused it to be preserved. Upon the publication of Sanarelli's description of the results of his experiments, Dr. (then Surgeon-General) Sternberg directed Major Walter Reed and the writer to undertake experimental work with Bacillus X, and later with *Bacillus icteroides,* for the purpose of comparison and identification, if possible. After working with these bacilli for several years it was concluded[3] that Bacillus X belonged to the colon group and *Bacillus icteroides* to the hog-cholera group; that the effects of inoculation of the smaller laboratory animals with *Bacillus icteroides* were the same as with *Bacillus cholerœ suis;* that the same lesions and clinical symptoms were produced in dogs by intravenous inoculation with either organism; that *Bacillus icteroides* when fed to young hogs pro-

[1] *New Orleans Medical and Surgical Journal,* 1848, vol. iv, pp. 580 and 581.
[2] *Yellow Fever and Malarial Diseases,* Greensville Dowell, M. D., Philadelphia, 1876; p. 13.
[3] Reed and Carroll, *Journal of Experimental Medicine,* vol. v, No. 3, December, 1900.

duced a necrotic enteritis differing in no respect from that induced by feeding to them pure cultures of *Bacillus cholerœ suis;* that by means of animal inoculations with these organisms sera could be obtained which gave a reciprocal agglutinative reaction; and, finally, the dried blood obtained from yellow fever patients exerted practically no agglutinative effect upon *Bacillus icteroides.* Sanarelli had prepared with his *Bacillus icteroides* a supposed curative serum for yellow fever; this was found to agglutinate both *Bacillus cholerœ suis* and Cushing's Bacillus O, the latter a member of the paratyphoid or enteritidis group, in high dilution.

The finding of *Bacillus icteroides* was confirmed by Archinard and Woodson in New Orleans; by Agramonte in Cuba, and by Bandi and others working in Brazil. Wasdin and Geddings, in an elaborate report, declared that infection in yellow fever took place through the respiratory tract; that *Bacillus icteroides* as the causative agent was present in the blood in nearly every case, and that cultures made from the blood early in an attack would establish the diagnosis. They inoculated monkeys, rabbits, guinea-pigs, rats, and mice, with pure cultures of *Bacillus icteroides,* and concluded that the infection which resulted was yellow fever.

Although persistent efforts are still made by one or two writers to sustain the claim of Sanarelli for *Bacillus icteroides,* the best European and American authorities now uphold the finding of the American Army Commission, that it was a secondary invader only.

In 1903 a Commission of the United States Public Health and Marine-Hospital Service described an organism which they designated *Myxococcidium stegomyiæ,* and suggested that it might be the etiological agent of the disease. It was shown within a few months, by experiments, that this was a blastomycete, and that it could be introduced into mosquitoes by feeding to them pure cultures of a wild yeast obtained from bananas.[1] The French Commission also regarded similar bodies found by them as yeast cells.

In the year 1900, during the American occupation of Cuba, a commission composed of Drs. Walter Reed, James Carroll, Aristides Agramonte, and Jesse W. Lazear, of the United States Army, was formed on the Island of Cuba to investigate the subject of yellow fever. In a report published in the month of October of the same year they stated that they had been unable to find *Bacillus icteroides* present in 29 cases (from 18 of which cultures were made during life and from 11 at autopsy), that *Bacillus icteroides* was not the cause of yellow fever, and that the mosquito served as the intermediary host for the parasite of the disease. After abandoning the search for *Bacillus icteroides* they had decided to put the mosquito theory to the test, and for this purpose they secured a number of volunteer subjects, among them two members of the commission, another contract surgeon named Pinto, and later, for other experiments, some soldiers and Spanish immigrants. Finlay had already claimed to have produced yellow fever with mosquitoes kept from two to six days after biting a patient, and the mosquito suggested by him was the one used in making the tests.[2] Experi-

[1] Carroll: "The Etiology of Yellow Fever; An Addendum," *Journal of the American Medical Association,* November 28, 1903; and Report of the Working Party No. 2, of the U. S. Public Health and Marine-Hospital Service, Bulletin No. 14 of the Yellow Fever Institute, Washington, 1905.

[2] Dr. Charles Finlay,* of Havana, was the first to propound clearly a mosquito theory of the transmission of yellow fever, though an insect theory, which was made to include the mosquito especially, as well as certain other insects, was advanced

ments were begun by Dr. Lazear in the month of August, 1900, with mosquitoes kept from two to thirteen days after contamination, applying them to 9 individuals, without success; but in the 2 last cases, using the same mosquito kept twelve and sixteen days, respectively, the attempts were successful.[1] In September, Jesse W. Lazear, a member of the commission, knowingly permitted himself to be bitten again by a stray insect in a yellow fever hospital while he was applying other mosquitoes to patients. He was bitten on September 13th, sickened on the 18th, and died on the 25th, after he had succeeded in showing in two other persons that the mosquito could convey the infection. He obtained immediate confirmation of his first case by applying the same mosquito at once to a second individual, on the day that the writer was taken ill. This second case also proved positive within five days after inoculation.

In order to further confirm and perfect the results obtained by Lazear, an isolation camp was established two months later, and named in his honor Camp Lazear. In this camp there were placed two physicians, one an immune, the other a non-immune, with a number of soldiers and some Spanish immigrants, all of whom had expressed their willingness to submit to the experiments, and after a sufficient period of strict quarantine the following confirmatory tests were made: *First*—Fifteen mosquitoes that had previously bitten patients with yellow fever were liberated in a mosquito-proof building especially constructed, and which had been divided by a wire-screen partition, extending from floor to ceiling, into two compartments, each of which was furnished with a bed that had been previously disinfected. The mosquitoes were liberated into one compartment and this was entered soon after by a non-immune, who, lying down upon the bed and exposing his chest and limbs, was bitten by several of the insects. He returned again for a short time on the same day, when he was again bitten by some of the insects, and on the following morning several more attacked him when he entered the third time for only a few minutes. This man became ill with a typical attack of yellow fever on the fifth day after he first exposed himself to the mosquitoes. On the evening of the day that this subject first entered the mosquito compartment, two other non-immunes were admitted to the opposite section, where they slept for eighteen consecutive nights, separated from the mosquitoes only by the wire screen partition. Their health was not disturbed in the slightest degree by this exposure. *Second*—Another mosquito-proof house was constructed and supplied with

and ably supported by Nott, of Mobile, Alabama, in 1847. In 1876, Dowell, of Galveston, Texas, again called attention to the fact that the gnat and mosquito were governed by the same natural laws as yellow fever. A number of observers had previously noted the unusual prevalence of mosquitoes during epidemics. Finlay attempted to prove his theory, but could not have succeeded, as he claimed to have done, because his mosquitoes were kept only two to five days (in one case six days), after biting a patient.† The cases that occurred among his subjects were clearly the result of the great prevalence of the disease in Havana at the time, and his tests were made without the special precautions necessary to guard against accidental infection.

* *Anales de la Academia de Ciencias Medicas de la Habana*, Habana, xxvii, 1890-91; p. 501.

† Carroll: "The Transmission of Yellow Fever," *Journal of the American Medical Association*, May 23, 1903.

[1] "The Etiology of Yellow Fever—A Preliminary Note," by Reed, Carroll, Agramonte, and Lazear. Proceedings of the American Public Health Association at the 28th Annual Meeting, Indianapolis, Ind., in October, 1900.

several boxes of soiled articles of bedding and clothing direct from the yellow fever hospital in the city. These articles had been intentionally soiled with urine, fæcal matter and black vomit obtained from fatal and other cases of yellow fever. This house was entered for twenty-one consecutive nights by two soldiers and a contract surgeon, non-immunes, who, after unpacking the boxes, handled and shook the soiled articles, hung them upon nails in the walls, and then retired for the night. In the morning upon rising they removed the garments from the walls, handled them again, then folded them and replaced them in the boxes. This performance was continued daily; the individuals remained in strict quarantine and were confined to the camp, but were permitted to spend the daytime in a tent set apart for the purpose, every night during the experiment being passed within the house and in the manner mentioned. At the end of three weeks this party was relieved and another party consisting of two non-immunes occupied the house in the same way, after the addition of a fresh supply of contaminated articles received from the hospital. They, likewise, in the same way, repeated the unpacking, handling and repacking the soiled articles for twenty-one nights and none were infected. Newly soiled articles of bedding and clothing had been added from time to time, and after the receipt of another supply upon their release, two additional non-immunes slept in the house for twenty-one nights longer. These men passed their nights within the identical garments and between the same sheets that had been used by patients dying of yellow fever. One of them slept with his head upon a towel soiled with blood drawn from a patient in the first day of the disease, and which was shown by inoculation to be capable of infecting. Notwithstanding these exposures these men also came out of the experiment building in perfect health, and they had increased in weight. The majority of the men thus exposed were afterward inoculated by means of mosquitoes or by blood injections, and their susceptibility was proved by their becoming infected. This was deemed sufficient to show that susceptible persons might live and sleep in intimate contact with fomites from yellow fever patients and suffer no harm as long as they were not bitten by contaminated mosquitoes. During the whole of this time the building was kept darkened; it was heated during the day to about 90° F., and the atmosphere was kept moist like that of the hold of a vessel in the tropics. It was thoroughly protected by copper-wire screens and double screen-doors against the entrance of mosquitoes. *Third*—In addition to these experiments men were singled out in certain tents within the camp, and to these contaminated mosquitoes, that had been kept sufficiently long, were applied, with the result that many of them contracted the disease. In every case the attack followed within the usual period of incubation, and no other persons in the camp became infected than those who were purposely inoculated. Every precaution was taken, a strict quarantine was maintained, and the residents of the camp were required to sleep always beneath mosquito netting. It was shown by these experiments that mosquitoes were capable of communicating the infection as long as fifty-seven days after they had bitten a patient suffering with yellow fever. *Fourth*—It was further demonstrated that the subcutaneous injection into a non-immune of 2.0 cc., 1.5 cc., 1.0 cc., or 0.5 cc., of blood drawn directly from the vein of a yellow fever patient in the first or second day of the disease would promptly cause an attack of yellow fever.

In the beginning twelve attempts at inoculation with mosquitoes which had been kept from four to eighteen days after biting the patient all resulted in failure; but the insects used for these tests had been kept at room temperature during the months of November and December. In January there was another failure resulting from the application of twelve mosquitoes kept for twenty-two days at a temperature of 82° F. after they had bitten a very mild case in the eighth hour of his attack. Yet ten persons in all were infected by the application of mosquitoes during the winter, and the other experiments made were deemed to show conclusively that fomites cannot transmit the disease; that yellow fever can be communicated by means of blood injections; that an infected house is simply one that contains "ripe" infected mosquitoes; and that the mosquito is harmless until twelve days or longer after it has bitten a patient, but that it retains the power to infect as long as it lives.

The first to confirm the efficiency of the mosquito as the transmitting agent of yellow fever was John Guiteras, of Havana, who, in the spring of 1901, succeeded in infecting a non-immune Spaniard by applying to him a contaminated mosquito obtained from the writer. In August of the same year Guiteras again succeeded in producing 7 additional cases, 3 of which were fatal; and immediately after this it was demonstrated independently by a member of the Army Board (Carroll) that the diluted blood serum from a patient suffering with yellow fever is capable of conveying the disease when injected subcutaneously in quantities of 1.5 cc. after having been passed through a new, sterilized Berkefeld filter.[1] It was further shown at the same time that the blood of a patient could be deprived of its power to infect upon subcutaneous inoculation by previously subjecting it to a temperature of 55° C. for ten minutes.[2] In this work six additional experimental cases were produced, and all recovered, making a total of twenty-two cases intentionally inoculated with yellow fever by the Army Board, without a death.

The first and second series of experiments above described formed the basis for the measures that proved finally successful in the hands of Gorgas in ridding Havana of yellow fever. Similar measures were undertaken in Rio de Janeiro, in 1903, but owing to the peculiarly unfavorable political and local conditions, and the lack of power to enforce them, they have not yet accomplished the desired result.

The doctrine of the transmission of yellow fever by the mosquito has now become firmly established through the confirmations of the work of the American Army Commission, by Guiteras of Havana, Ribas and Lutz of Brazil, the French Commission from the Pasteur Institute, working also in Brazil, Working Parties No. 1 and No. 2 of the United States Public Health and Marine-Hospital Service, at Vera Cruz; and, we may add, the experiences of Laredo, Texas, in 1903, of Mexico in 1903–05, and of New Orleans in 1905. Marchoux, Salimbeni and Simond, the members of the French Commission, concluded that yellow fever is contracted in no other way than through the bite of the mosquito *Stegomyia fasciata;* that

[1] Reed and Carroll: "The Etiology of Yellow Fever: A Supplemental Note," *American Medicine,* vol. iii, No. 8, p. 301–305.

[2] This experiment was subsequently repeated at Rio de Janeiro by the French Commission, who succeeded in reducing the time of exposure at the same temperature to five minutes.

to become capable of infecting, the mosquito must bite a patient during the first three days of the disease, and that the mosquito is harmless until the lapse of at least twelve days after biting a patient; that no other mosquito than *Stegomyia fasciata* aids in the transmission of yellow fever; that simple contact with the patient, his personal effects, garments, or excreta, will not communicate the disease; that yellow fever can become epidemic only in places where the mosquito exists; and that prophylaxis against yellow fever rests entirely upon the means taken to prevent mosquitoes from biting the sick and the well. They make the seemingly important statement that the period of incubation of yellow fever may be prolonged to thirteen days; but since in all cases in which a period of incubation longer than six (plus) days has been obtained the subjects of these prolonged periods of incubation had been previously injected with blood or serum from persons who were suffering or had suffered with yellow fever, we question the practical importance of such prolonged periods of incubation, resulting evidently from experimental interferences; and we believe that for practical purposes they may, with safety, be ignored.

The work of the French Commission in Brazil stimulated the sanitary authorities of Rio de Janeiro to adopt means for the suppression of the disease similar to those that had proved successful in Havana. The difficulties they encountered were almost insuperable from the unfavorable local sanitary conditions, the political opposition, and the ridicule to which they were subjected by the local press. Nevertheless they acted upon their convictions, supported by the authorities after a campaign of education among the people, and, although the disease is not yet conquered, much has been attained, and the outlook for the future is very bright. Indeed the measures taken in Rio in 1903 were far ahead of those instituted in our own country at Laredo and New Orleans until the situation was taken in hand by the central government. The most striking results have been obtained in Mexico, in Texas, and in New Orleans, where yellow fever has been stamped out before the appearance of frosts by measures directed solely against the mosquito.

In Mexico yellow fever has been eradicated from its endemic focus at Vera Cruz through the able efforts of Edouardo Liceaga, the President of the Superior Board of Health, whose complete grasp of the problem and whose enlightened and energetic action has added support to the mosquito doctrine, and would have controlled the disease absolutely if the same means of enforcement were available in Mexico as in Cuba in 1901. Finally, in New Orleans during 1905 with an epidemic beginning earlier in the season than usual, with a larger non-immune population than ever before, and with the disease well established early in August, great success was attained in ultimately controlling and stamping out the epidemic before its disappearance could be attributed to the occurrence of frosts. These successes have encouraged the persons in authority and converted the majority of the local physicians, so that in New Orleans, where formerly the mosquito theory was treated lightly, physicians, and particularly those in the outlying districts, are thoroughly convinced from practical observation, and are prepared to institute decisive and effectual measures upon the appearance of the first signs of another outbreak. Could the permanent endemic foci in Rio de Janeiro and in some of the smaller Central American republics be once destroyed by intelligent and systematic efforts, the United

States and Mexico would then be freed from the danger of repeated invasions of yellow fever, and concerted action on the part of all the countries concerned would make it an easy matter to insure the complete suppression of the disease and immunity for the future.

Notwithstanding all the efforts that have been put forth in that direction, the specific organism of yellow fever still awaits recognition.[1] The arguments opposed to the idea that the invisible causative agent of yellow fever is a bacterium are: (1) it has never been recognized nor cultivated; (2) according to the French Commission the blood of a patient loses its power to infect within two days if exposed to the air, and within five days if air be excluded; (3) the absolutely non-contagious and even non-infectious character of the disease under conditions otherwise favorable but in the absence of the mosquito. The arguments in favor of its being a member of the animal kingdom are: (1) its obligatory parasitic existence in man and the mosquito, alternately; (2) the necessity for the lapse of a definite period, two weeks or more after the ingestion of the blood, before the mosquito becomes capable of infecting; (3) the restriction of the hosts to a single vertebrate and a single genus of invertebrates which points to a definite cycle of development; (4) the rapidity of development of the parasite within its invertebrate host is governed by conditions of external temperature in the same way as the rate of development of the malarial parasite in the anopheles mosquito.

Before dismissing this part of the subject let us remember that great credit is due to ex-Surgeon-General George M. Sternberg, whose work in the study of the bacteriology of yellow fever has never been surpassed. The labors of the American Army Board were undertaken at his instigation and by his direction and they were the direct outcome of his continued and absorbing interest in the subject.

Susceptibility.—All races are not equally susceptible; the white races, and especially those with fair skins and who inhabit northern climes, appear to suffer most. The negro is susceptible but not in the same degree as members of the white races. The relative immunity of the negro is not due to any protection he enjoys against the bites of mosquitoes, for a hungry mosquito of the genus Stegomyia will attack a black negro in the axilla as readily as she will sting a white person.[2] One attack of the disease generally confers permanent immunity and second attacks are rare. It is quite possible that a person after recovering from a very mild attack would again become susceptible after a lapse of time. The incidence of the disease is greatest in young adult life, and the mortality rate is higher among those who are already debilitated from any cause. There seems good reason to believe that the immunity enjoyed by the inhabitants of countries where the disease has become endemic probably results from mild infections during infancy and childhood. This role has been attributed to the borras fever of children in Cuba.

[1] Recently H. Wolferstan Thomas, *British Medical Journal*, January 19, 1907, has reported that a chimpanzee had been infected with yellow fever in Brazil by permitting it to be bitten by twenty-nine mosquitoes, twenty-one days after they had been fed once upon a patient with typical yellow fever in the second and third days of the disease. The period of incubation was three days and the course of the attack quite typical of that of a mild case of yellow fever, including the presence of albumin, bile pigment and blood in the urine.

[2] Actual experiment.

Special Pathology.—Yellow fever is a general infection with severe intoxication. The most marked effect of the toxin is seen in the liver, the probable reason being that the toxin possesses a marked affinity for the hepatic cells. From the clinical manifestations we would infer also that there is some affinity between the toxin and the cells of the central nervous system and perhaps those of the muscular system in general, as well as the vascular endothelium. The ghastly lesions in the digestive tract are chiefly mechanical in origin and secondary to those in the liver; it is difficult to say to what extent the lesions found in the kidney after death are due to the toxin of the disease and how much to secondary intoxication resulting from damage to the liver.

Rigor mortis appears early and is very marked. When death takes place on the eighth or ninth day, the skin of the trunk is usually of a canary-yellow color. This is less intense on the extremities, but the eyeballs are deeply tinted and the face is distinctly yellow, mingled with the natural coloring of the skin. The intensity of the color varies usually with the stage and severity of the attack. The dependent parts of the body are deeply discolored and livid, and the same is true of the tips of the fingers and toes, scrotum, penis, etc. Livid patches may be present on the upper surfaces of the body and the face. These appear soon after death, and the face may even be bloated and livid before death. The fat and connective tissues are tinged with bile. Hemorrhages beneath any or all of the serous membranes are frequent. No constant lesions are found in the brain and spinal cord. The vessels of the pia mater and brain substance are usually engorged, and hemorrhages frequently take place into the brain substance and beneath the membranes. A yellow or reddish serum may be found in the lateral ventricles.

The lungs are the seat of marked hypostatic congestion, with hemorrhage; and hemorrhages are often visible beneath the pleural membrane. The heart is distended; its muscular tissue is of a deep reddish-brown color and sometimes softened in consistency, but this is not constant.

Digestive Tract.—The stomach may be found distended with black, fluid blood, even in cases in which black vomit did not appear during life. Before the stomach and intestines are opened, dark slate-colored areas may indicate the presence of this material within. After removing and washing the stomach, its mucous membrane may be found to be pale and eroded, or blood stained. At the pyloric end there is congestion of its mucosa, as a rule, and there may also be found large areas of diffused submucous hemorrhage. The mucous and submucous layers are more or less thickened according to the degree of congestion and the amount of hemorrhage that has taken place; and the larger veins are distended with dark blood.

The mucous membrane of the duodenum is always deeply congested, swollen, and the seat of hemorrhages. The condition of the jejunum and ileum depends upon the duration and severity of the attack. The upper part of the jejunum is usually involved with the duodenum, and the congestion may continue for some distance into the ileum. On the other hand, the ileum may appear practically free from any pathological lesion after the contained blood has been removed. The passive damming up of blood in the mesentery and intestine, which results from compression of the capillaries by the swollen liver cells, is manifested earliest and with the greatest intensity in the pylorus and duodenum, because here the communicating

vessels are short, there is little or no anastomosis, and the pressure cannot relieve itself by becoming distributed over a large area. For this reason the passive congestion is always more marked in this region (duodenum) than lower down, and it may be regarded as invariably accompanying the disease, even in its mildest form. This is probably the true explanation of the presence of exquisite tenderness upon deep pressure in the epigastrium, a valuable sign in the diagnosis.

The liver is tense, firm, and smooth, showing that its cells are swollen. The color of the organ is variable. It may be uniform or mottled in appearance, but it is always yellowish or brownish in color and usually shows areas of congestion or hemorrhages beneath the capsule. Upon section the organ is firm, pale, and friable. The cut surface also may be either uniform or mottled. The most distinctive features are found upon examination with the microscope, though similar conditions are present occasionally in other fatal infections. There is a remarkable alteration in the normal arrangement of the liver cells, which no longer present the uniform regularity that belongs to the normal tissue, except in certain linear areas bordering on the portal spaces. In general they show marked variations in size and their normal outlines are distorted. The majority are densely packed with medium-sized fat droplets, and the protoplasm of some is coarsely granular and stands out conspicuously in sections counterstained with eosin. The majority of the nuclei are swollen, pale or obscured, and it is notable that although in certain areas small hemorrhages may be found, the lobular capillaries in general are compressed by the swollen hepatic cells. The degree of fatty degeneration is somewhat variable, but it is always present in remarkable degree; in certain instances practically all the lobules are affected throughout, while in others whole lobules or small areas may escape destruction. These differences can be explained perhaps on the theory that some patients are overwhelmed and succumb early, while in others the destruction of liver cells proceeds more deliberately and is more complete when death takes place. The jaundice, which results from the pressure of the swollen liver cells upon the smaller biliary vessels, is, of course, hepatogenous and not hæmatogenous in origin. Hyalin bodies that stain brightly with eosin have been described by Councilman as lying within the liver cells and between them.

It is proper to consider here the effect of the damage inflicted by the toxin upon the hepatic cells from the point of view of its effect upon the elaboration of urea and the ultimate result upon the secretion of urine. In the excessively degenerated condition of the liver in the advanced stages of severe attacks but little urea can be formed, and the carbonate, carbamate and lactate of ammonium (end products of cell metabolism), being no longer converted by the liver into urea, are retained in the circulation and act as additional poisons. There are thus produced two serious complications, anuria and ammonæmia. It is a matter of common observation that urea is deficient in the urine in yellow fever, and this occurs because the liver no longer provides the normal quantity of urea, and not because the kidneys fail to secrete it. The delirium and coma (with or without convulsions) seen in fatal cases of yellow fever are due to ammonæmia and not to uræmia,[1]

[1] See author's "Note on the Treatment of Yellow Fever," in the *Journal of the American Medical Association*, July 19, 1902.

and by the early elimination of toxin we lessen the degree of fatty degeneration of the liver and diminish the tendency to anuria, to severe intestinal hemorrhages, and to the ammonæmic intoxication which is necessarily superadded in the fatal cases.[1]

Kidneys.—The condition of the kidneys is more variable than that of the liver because involvement of these organs is not so general or so intense. In the fresh condition the kidney is of normal size or slightly swollen, pale, and fatty, or congested. In sections examined under the microscope there is usually found a condition of acute diffuse nephritis; the lesion is sometimes of a distinctly degenerative type; at others it consists of not much more than a well-marked cloudy swelling. There may be found hyaline droplets within the tubules and capsules of Bowman, and these or the swollen capillary endothelium may have undergone calcareous infiltration. The glomeruli may be swollen and engorged or atrophied; the capsular epithelium may have suffered but little change, or it may have become swollen or degenerated, or have entirely disappeared. One is frequently impressed with the fact that the lesions are relatively less severe in the kidneys than in the liver.

Spleen.—The spleen may or may not be enlarged and soft, but it is always congested. The swelling, when present, is probably due to the presence of bacteria as secondary invaders, from the intestine or other mucous surfaces.

The microscopic evidences of enteritis (emigration of polymorphonuclear leukocytes, etc.) found in some cases are due, no doubt, to an invasion by bacteria from the lumen of the intestine.

The old idea that the blood undergoes degenerative changes in yellow fever is without foundation. In the later stages many of the leukocytes may contain minute fat droplets or vacuoles, and there may be some anæmia; but in the early stage there is no marked anæmia, no cell destruction, and the leukocytes are practically normal in number and appearance. In a small proportion of the cases a moderate degree of polymorphonuclear leukocytosis can be demonstrated.

Symptoms.—The earliest symptoms may be a premonitory feeling of malaise, with pain in the back and loins, or a slight frontal headache. There is usually a furred tongue, with constipation. In the majority no marked premonitory symptoms are noted.

At the onset there may be a sudden chill or rigor occurring at night or during the day. The patient may have lost his appetite and have gone to bed to rest and sleep in the middle of the day, to wake up later with high fever. With the onset of fever there is a sharp headache, generally frontal, but occasionally occipital in location; the face is flushed, the eyes injected, rachialgia is often present, and the temperature may range anywhere from 102° to 106° F. or even higher. In mild cases the skin is moist; in severe ones dry and hot; constipation is usually present; the tongue is clean or lightly coated and its tip and edges red; photophobia may be pronounced or absent; the pains may be agonizingly severe or very mild in character;

[1]Aitkin states that "the presence of ammonia in black vomit is universal, and may be considered as one of its tests"; and that "carbonate of ammonia is frequently found in the breath, in the normal black vomit, almost always in the stool, and that it apparently pervades all the tissues of the body." *The Science and Practice of Medicine*, London, 1880; vol. i, p. 651.

nausea may be absent, but usually it is present and followed by vomiting of a clear colorless or yellowish or greenish fluid. The symptoms are all more or less pronounced, depending upon the character of the attack. There may be great epigastric distress and the amount of urine passed may be small, but no albumin is found. At this stage the case resembles one of acute malaria, typhoid fever, or any severe infection. A blood examination will exclude malaria; the locality and other circumstances will determine the probability of yellow fever; if the eyeballs display a yellowish tinge, as they rarely do at the onset, there is strong ground for suspicion. On the second day the temperature may remain elevated or a fall may be observed; the headache and body pains may have abated or they may continue; the photophobia is more marked; the flushing of the face and ocular injection are pronounced; a slight yellowish tinge of the eyeballs can be distinguished. The stomach may be quiet, or the nausea and vomiting may be distressing but somewhat abated. There may be suppression or retention of urine, requiring the use of the catheter. The skin of the chest is of a dusky hue, and upon pressure it is seen that the capillary circulation is sluggish. On the third day the temperature may remain about the same or fall several degrees and then rise to near its original height, or it may fall gradually and decline during several days by lysis. A sudden drop in temperature to subnormal, with the appearance of black vomit and suppression of urine at this time, almost certainly means a fatal issue. More frequently, after a brief decline on the second day, the temperature rises gradually to 103° or 104° F. and remains there with a morning fall of one or two degrees for one, two, or three days, and then declines gradually to normal. Vomiting may return and the material ejected may contain fly-wing specks or coffee-ground granules, or it may consist of the brownish or brownish-black fluid known as black vomit. The jaundice is now (fifth or sixth day) quite intense, great weakness and prostration are manifested; there may be cramping pains in the abdomen, with the passage of a large amount of tarry material; these may be accompanied or followed by persistent hiccough, delirium, convulsions, coma, and death. The remission or intermission in temperature may occur after twenty-four, forty-eight, or seventy-two hours. In mild cases the occurrence of a distinct remission or intermission may be questioned.

Faget's Sign.—Following the remission or intermission, a singular and progressive diminution occurs in the pulse rate, so that with the secondary exacerbation of fever there is the anomaly of an ascending temperature with a slowing pulse, and this continues regardless of the temperature. With the appearance of jaundice, at this time, the pulse rate diminishes to 70, 60 or even 50 per minute. In well-marked cases this is a valuable and fairly constant diagnostic sign, but in the milder cases the lack of correlation between pulse and temperature is much less apparent.

We find the same variability in the severity of different attacks of yellow fever as in measles, scarlet fever, or any other disease. Nothing could be more accurate than the following statement of Nott:[1] . . . "In the same family and house, one will be so lightly attacked as scarcely to lie down, while another is dying with all the horrors of black vomit; and, what is particularly worthy of note, the light cases pass off spontaneously in two

[1] *New Orleans Medical and Surgical Journal*, 1848; vol. iv, p. 586.

or three days *without a dose of quinine, and afford protection against the disease in after years.*"

Epistaxis may be present early, but a more reliable sign is the condition of the gums. At the beginning of the fever they may be swollen and spongy; a day or two later a red line is seen at the margins and upon gentle pressure blood can be made to exude. In severe cases the oozing may be constant and sufficient to stain the lips and tongue. As the disease progresses the tongue becomes, at first lightly, then heavily, coated, and later it may become fissured and bleeding so that the saliva, lips, and tongue, are all blood-stained. The coating on the tongue may become dark and even black in color. Hemorrhages from the mucous membrane of the mouth, nose, intestine, and genito-urinary tract (especially in females) are frequent after the fifth or sixth day. They are due to blood stasis in the capillaries and degeneration of their endothelium, both of which are direct or indirect results of the action of the toxin.

Skin.—The skin of the face and chest may bear a blotchy or clean petechial eruption in mild as well as in severe cases, and the appearance may resemble that of a mild eruptive fever. Small macules, papules, pustules, or blebs, may appear after the disease has developed. If these become hemorrhagic the outlook is serious.

Urine.—In a case of moderate severity the microscopic examination will show the presence of tangled masses of hyaline threads at the outset, when the kidneys are only congested. After a day or two hyaline and finely granular casts appear, and on the fifth or sixth days there are coarsely granular and epithelial casts, which show a more or less deep staining with bile pigment. Red blood cells may be present at about this time and may be scarce or abundant according to the tendency to hemorrhage. The intensely dark color of the urine, about the sixth or seventh day, is due to the presence of bile and not of blood, though it is not rare to find blood present. Polymorphonuclear leukocytes are always found in small number after the use of the catheter, and have no special significance unless they are numerous, in which case they indicate some complication, such as gonorrhœa, cystitis, nephritis, etc.

A trace of albumin will be found on the second or third day, and the amount may increase rapidly until the specimen coagulates upon being heated. The albumin usually disappears from the urine with defervescence, but either albumin or casts may persist for one or several months after the termination of severe attacks.

No chain of symptoms can be given that will cover all cases. Stress should be laid upon the point that some attacks are so mild as to appear almost trivial while others are rapidly fatal. Perhaps the best classification would be the following:—

Mild.	*Severe.*
Very mild.	Moderately severe.
Mild.	Severe.
	Very severe (including the fatal cases).

Diagnosis.—The period of incubation being from two to six days, usually from three to five, will aid in determining the probability of exposure in persons who present suspicious symptoms in places removed from the

habitat of the disease. The early suffusion of the face and eyeballs, vertigo, frontal headache, pain in the lumbar region and loins, pains in the extremities (chiefly the lower ones, but not involving the joints), nausea and vomiting, with ocular jaundice on the second day, should excite strong suspicion; and with the accompanying exquisite tenderness elicited by deep and gentle pressure in the epigastrium the diagnosis would be reasonably certain. The chill or rigor may be absent, the headache may be occipital, vomiting may not occur, and the temperature may not rise above 102° F. in a mild case. Malaria and most inflammatory conditions can be excluded by examination of the blood. In relapsing fever spirochætæ will be present in the blood during the febrile exacerbation; in typhoid fever the bacilli may be obtained in blood cultures; and in these infections albumin is not nearly as likely to be present in the urine on the second day as in yellow fever. Mild cases may be extremely difficult of diagnosis, but the knowledge of exposure and the symptom-complex, as a whole, with ocular jaundice on the second day, together with marked epigastric tenderness, would justify a provisional diagnosis of yellow fever in the absence of special contra-indications. Faget's sign, albuminuria, bloody oozing from the gums on pressure, and fly-wing material in the vomitus, would render the diagnosis complete. In the severer cases the diagnosis becomes clear by the third day at the latest.

A sudden fall in the temperature to subnormal in the first few days, suppression of urine, hiccough, black vomit, and free intestinal hemorrhages, are all indicative of grave attacks. For diagnosis the extreme tenderness on deep gentle pressure in the epigastrium is a point of great value, and the examination must be made with the utmost care, for unnecessary pressure may cause intense suffering. The capillary hemorrhage from the gums, pulse phenomenon, and early jaundice, make the diagnosis comparatively easy in well-marked cases in a region where the disease is known to prevail. If there be a possibility of error it should be thrown on the side of safety, for it is better to take extreme precautions with a case that subsequently proves not to be yellow fever than to find when it is too late that if certain precautionary measures had been adopted with cases apparently not yellow fever, an epidemic would have been averted.

Guiteras[1] has recently called attention to some valuable aids in the diagnosis of doubtful cases. He believes that Ehrlich's diazo reaction is practically never present in uncomplicated cases of yellow fever, although it may be present in severe cases of dengue. He has been able successfully to exclude yellow fever by obtaining the Ehrlich diazo reaction in the urine. He lays special stress upon the value of the estimation of hæmoglobin, the percentage of which in yellow fever is rarely below 90 in the first three, four or five days. He states that if the percentage is found to be below 80 in the first few days in a case of yellow fever some complication will always be found or the patient will have previously suffered from malaria.

A point of great importance in the differential diagnosis between dengue and yellow fever has been brought out recently by Van der Berg,[2] who states that in dengue there is a leucopenia, the leukocytes being reduced on the average about one-half. Stitt,[3] working in the Philippines, confirms the statement in regard to dengue, in which he finds a polymorphonuclear as

[1] *Medical Age*, Detroit, vol. xxiv, No. 6; March 25, 1906.
[2] Mense's *Handbuch der tropenkrankheiten*, Leipzig, 1905; vol. ii, p. 98.
[3] *Philippine Journal of Science*, vol. i, No. 5; June, 1906.

well as a general leukopenia, with a marked relative increase of the mononuclear leukocytes. This is in marked contrast to the condition of the blood in the early stage of yellow fever, in which the total leukocyte count is practically normal and there is no diminution in the proportion of polymorphonuclear leukocytes; on the contrary they are frequently increased.

Prognosis—In every case of yellow fever, no matter how mild, the prognosis must be guarded. Even in those which are apparently trivial, grave symptoms may develop after errors in diet, permitting the patient to leave his bed, or failure to maintain the eliminative functions. A quiet stomach, low temperature, soft velvety skin, the ability to sleep, and a free flow of urine, are all favorable. High temperature without remission, intense and persistent headache, nausea, and nervous irritability, indicate a more serious condition; a temperature above 105° F., delirium, singultus, black vomit, partial suppression of urine, convulsions, dark petechial spots, and hemorrhages into the skin or intestine, are of grave significance. Complete anuria, free intestinal hemorrhages, profuse black vomiting, with hiccough and coma, are signs of fatal import.

Mortality.—Under favorable modern conditions the mortality rate from yellow fever should not exceed 10 or 15 per cent.; it should never exceed 20 or 25 per cent. under any circumstances, and a higher death rate would warrant the suspicion that the milder cases were escaping recognition. Now that the diagnosis of "bilious remittent fever" can be excluded, the fact is becoming more apparent that a fairly large proportion of cases of yellow fever are mild in character and recover without black vomit. In some of the fatal cases this symptom is absent, but the blood is always present whether it is ejected or not.

Sequelæ.—But few sequelæ follow yellow fever. Recovery takes place quickly, as a rule, and the patient rapidly regains weight and strength. In a small number recovery is followed by a period of weakness and debility which may persist for one or two months. Suppurative inflammation of the parotid and other glands, abscesses, and furuncles, are the only sequelæ that deserve mention, and these yield slowly to the ordinary measures as the patient's strength and vitality improve.

Treatment.—Hygienic and Prophylactic.—The most important duty of the physician during an epidemic, or in the possibility of an epidemic of yellow fever, is to institute preventive measures tending to guard against extension through the agency of the mosquito, and it is necessary to see that proper precautions are taken by non-immunes to insure them against the chances of being bitten by mosquitoes that are possibly infected. *Stegomyia fasciata* is a twilight mosquito that feeds, as a rule, early in the morning and in the afternoon until ten o'clock at night It usually rests in the middle of the day, when free to follow its own inclinations, and non-immunes may visit well lighted places in infected localities between 9 A.M. and 3 P.M. with almost absolute impunity. But at 3 P.M. the danger begins, and after this hour one should go to high localities without the infected city, or retire within a building thoroughly protected by wire screens against the entrance of mosquitoes. This will afford the maximum degree of protection, and in order to lessen the danger by reducing the number of mosquitoes present every precaution should be taken against the accumulation of standing water in surface pools, gutters, tubs, barrels, rain-water spouts, pitchers, vases, or other receptacles, either indoors or for some distance

without a dwelling. The use of petroleum and wire-screen covers, when required, with an occasional fumigation by means of pyrethrum, will add to the comfort and security of non-immune persons in an infected district. In regard to the sick, all persons in an infected locality suffering from fever of unknown origin, particularly if it begins with a chill and headache, should be isolated at once and placed behind mosquito-proof wire screens and mosquito netting. The net should be tucked in beneath the mattress, and it should be remembered that the mosquito on the outside can easily bite the face or an extremity lying against the net. These precautions should be continued until the temperature remains normal. As soon as a patient suffering with yellow fever is removed from a room, it should be tightly sealed by pasting paper over all cracks and openings and then fumigated with pyrethrum, using at least one-fourth pound to each one thousand cubic feet. After five or six hours the stupefied insects should be swept up from the floor and burned. Tobacco and sulphur are more efficient but more disagreeable than pyrethrum.

It is hardly necessary to state that although there is a general infection with involvement of the blood in yellow fever, disinfection of the person, effects and surroundings of a patient is useless, for we know that the disease is absolutely non-contagious. This, and the lapse of a definite period of time that is necessary before the mosquito can become capable of transmitting the disease, are convincing arguments against its bacterial origin, for if the specific agent were a bacterium it would certainly be transmitted from man to man, and would gain entrance to the body through mucous membranes. There is evidence to show, also, that physicians who cut themselves in dissecting the bodies of persons dead of yellow fever do not become infected.[1]

A quarantine period of at least five days is necessary, and measures should be taken to protect ships against the entrance of mosquitoes when lying at infected ports. One-fourth of a mile is a safe distance from shore, and the proximity of other vessels should always be avoided.

Unnecessary stress seems to have been laid upon the danger of yellow fever being conveyed to the Orient by vessels passing through the Panama canal after its completion. The modern iron or steel vessel does not furnish the favorable conditions for breeding mosquitoes that formerly existed upon the old wooden sailing vessels, upon which fresh water was stored in wooden casks, and the rules of cleanliness much less rigidly enforced than to-day. With the knowledge now in our possession of the domestic habits of *S. fasciata*, and the power to easily prevent the access of the mosquito to vessels by compelling them to anchor at a sufficient distance from the shore or from other vessels; with the vigilance exercised by the officers of the United States Public Health and Marine-Hospital Service stationed at ports in the epidemic zone; with the custom of carrying a physician on the larger steamers; with the slight chances of an infected mosquito flying on board a vessel while in transit through the canal owing to the fact that yellow fever will not be permitted to flourish along the line of the canal; with the knowledge now generally disseminated that an outbreak of yellow fever on shipboard can be effectually stamped out by the use of mosquito netting and by fumigation, which would enable an ordinary steamer captain to protect his vessel and

[1] Thomas O'Halloran, M. D.: *Remarks on Yellow Fever*, London, 1823; p. 204.

crew should they become infected, the possibilities of such an accident as the infection of a port in Asia or Australasia seem very remote.

As a matter of personal prophylaxis non-immunes should never spend the night in an infected locality, though, as already stated, such places may be visited for the transaction of business with practically absolute impunity between the hours of 9 A.M. and 3 P.M. Should exposure after dark in such localities be unavoidable, then mosquito headnets, heavy gauntlets, and leggings should be worn, and upon retiring the person should see that mosquitoes are expelled from the room or destroyed by fumigation with pyrethrum, tobacco, or sulphur. The sleeping-room selected must be as high as possible above the ground; he must see himself that the bed and its vicinity are free from mosquitoes and perfectly protected by intact netting of 1.0 or 1.5 mm. mesh. It is unsafe to rely upon the local use of the essential oils, more or less diluted, spirit of camphor, etc., upon the skin. Experiments have shown that hungry mosquitoes will disregard such applications.

In the matter of general prophylaxis it is necessary to bear in mind that three factors are indispensible for the production of an outbreak,[1] *viz:* (*a*) preëxisting cases of the disease; (*b*) mosquitoes of the genus *stegomyia;* and (*c*) the presence of non-immunes. These are brought into play in the order stated, and in the absence of any one an epidemic is impossible. The most rational and effective mode of procedure, therefore, is to prevent the interaction of *a* with *b*; if this be effected, *c* may be disregarded. Failing to prevent the contact of *a* with *b*, then if *b* and *c* be permitted to come together after the proper interval, infection results, and can be brought about in no other way, without experimental inoculation. It is of the utmost importance, therefore, to insure complete safety during the epidemic season, in the infected zone, and all cases of fever, the cause of which is not at once apparent, should be removed without delay to a screened hospital in a location free from mosquitoes; or, as a less desirable alternative, the patient should be placed immediately either beneath mosquito netting or in a portable mosquito-proof cage, and behind properly screened doors and windows. The general destruction of mosquitoes during an outbreak should be made subsidiary to the first and primary end to be attained; namely, protection of the patient from mosquitoes from the very beginning of the attack, because, if contact of the patient with mosquitoes be prevented, the occurrence of secondary cases becomes impossible.

It is now an established fact that an interval of about two or three weeks *must* elapse after the importation of a first case before the appearance of secondary cases, and whenever the course of an outbreak is being traced in other than an epidemic locality, it can be safely taken for granted that whenever a group of cases is found to occur together the primary case from which the group originated must have existed two or more weeks earlier. If instead of a group only a single secondary case is produced, the difficulty will be very great, because it may be assumed that this was the primary case. The briefer period stated, two weeks, represents the shortest known developmental or incubative period (twelve days) in the mosquito, plus a short period of incubation in the human being.

The past history of New Orleans, Baltimore, and Philadelphia, shows that the plan proposed in Rio de Janeiro of housing the dock laborers in a

[1] Carroll: *American Medicine,* vol. ix, No. 22, June, 1905; pp. 907–915.

separate mosquito-proof building and keeping them under medical supervision during the warm season is a most desirable one, as long as they remain in direct communication with infected ports.

Medical.—The medical treatment of the patient suffering with this disease is also in a sense prophylactic, because by putting him to bed early and instituting proper treatment we can lessen the severity of the attack, and in some cases avert a fatal issue. That this can be done is clearly shown and must be accepted on the testimony of men of such great experience as Izett Anderson[1] and Just Touatre.[2]

It is of vital importance that the patient be put to bed and kept perfectly quiet upon the manifestation of the earliest symptoms. The bowels should be moved by a mild cathartic. Usually sulphate of soda[3] is the best, in doses of 4.0 grams (1 dram) every hour, until the desired result be obtained, or six doses have been given. If the bowel fail to respond within an hour after the sixth dose, an enema of plain soap and water should be given. The saline may be preceded by a small dose of calomel with bicarbonate of soda, 0.23 gram (3 grains) of each, or several minute doses of calomel at short intervals, if the stomach be irritable. Following the catharsis a hot mustard foot bath should be administered, and the patient should then be covered with blankets to induce free perspiration. This lessens the congestion of the kidneys and relieves headache and nausea. Hot lemonade may be given to aid diaphoresis. If the irritability of the stomach be not relieved a sinapism should be applied locally, and iced carbonated Vichy water in small quantities, or small doses of sodium bicarbonate, 0.2 gram (3 gr.), in a little ice-cold mineral water, administered. As soon as the patient has been made comfortable he should be permitted to sleep, the room being always kept darkened and free ventilation allowed, at the same time protecting him from drafts. The danger from drafts has probably been exaggerated in the past. All food must be withheld during the first three or four days, and the patient should be encouraged to drink carbonated Vichy water freely and often, and always ice-cold. If this is not at hand any of the alkaline mineral waters may be substituted, after adding about 2.0 grams (30 gr.) of sodium bicarbonate to the pint. The effervescing mixture of Anderson should serve an excellent purpose if mineral water cannot be obtained. He adds 30 grains of potassium bicarbonate to a dessertspoonful of freshly expressed and strained lime juice and gives it every two hours while effervescing. He is particular to state that it must be neither alkaline nor acid but neutral. Both Touatre and Anderson state that since their adoption of the Vichy water and effervescing mixture, respectively, they have ceased to see the profuse black vomit and hemorrhages they had formerly observed, and they both speak after more than thirty years experience with the disease. For the cephalalgia ice-cold applications are best; the pain passes off after a few hours—twenty-four at most. The coal-tar preparations and morphia should be avoided as a rule.

In the mildest cases the temperature may remain at about 100° or 101° F. for several days, reaching 102° once and then gradually declining to normal. In a severe case the temperature may ascend to 105° F. or higher at the out-

[1] *Yellow Fever in the West Indies*, London, 1898.
[2] *Clinical Notes on Yellow Fever*, New Orleans, 1898.
[3] Sodium sulphate is less disagreeable than the magnesium salt; it is milder and equally certain in its action, and in small doses is a diuretic.

set and again in the secondary exacerbation. Such cases require cold sponging every hour or oftener; or the wet pack or cold bath may be used to reduce the temperature and afford comfort. The former should always be tried first, and in the beginning, if the skin be dry and pungent, sweet spirit of nitre, in doses of 2.0 to 4.0 cc. (½ to 1 dram) in a little iced water every half or every hour until the skin becomes moist, may be given. The patient should be encouraged to drink alkaline waters freely, and if there be persistent nausea or irritability of the stomach, alkaline fluids should be given cold, by high rectal injection, permitting them to flow in very slowly to insure that they will be retained.

Food being withheld for the first three or four days, the patient should be supplied freely with the fluids already mentioned for the double purpose of allaying thirst and maintaining the renal secretion. Sodium bicarbonate when well diluted is bland, soothing to the stomach, and a mild diuretic. It is now thoroughly established that this salt exerts a markedly beneficial effect in yellow fever; whether it is because it remedies a deficiency of alkali or neutralizes an acid poison remains to be shown. After the third or fourth day, if the temperature continues below 101° F. and the patient craves food, he may be given a tablespoonful each of milk and lime water, cold toast water, or barley water, in small quantities and at rather long intervals at first, until the effect has been noted. Pure frozen cream, and gelatine in the form of wine or lemon jelly, are beneficial, and may be given in small quantities if they are enjoyed. After three days of normal temperature, if the patient's condition be good, he may be given milk, chicken broth, blanc mange, ice cream, or custard, and fresh juicy fruits, followed in a day or two by soft-boiled eggs, toast, chicken, etc.

Yellow fever is characterized by such marked depression with impairment of the circulation that stimulation is directly indicated. No other form of stimulant seems to equal a good dry champagne. It tends to allay nausea and vomiting, is mildly diuretic, and agreeably stimulating. It should be given in small doses of about 15 cc. (a tablespoonful) with ice, every two, three, or four hours, as indicated by the condition of the patient and its effect. It should be given on the second and third days of the fever only when the patient expresses a desire for it, and when the effect upon him is beneficial. Should the patient tire of champagne, Rhine wine or dry Catawba may be tried. The stronger alcoholic stimulants are not so desirable, but they may be used cautiously with persons who are accustomed to and prefer them. They should be well diluted.

The chief value of the alcohol is to aid the heart in keeping up the circulation and maintain the nutrition of the capillary endothelium. If at the outset we preserve the integrity of the vascular endothelium, keep the blood moving within the capillaries, and secure elimination of the maximum amount of toxin, then, if the heart, liver, and kidneys were previously sound, we prevent the occurrence of excessive hemorrhages, and the patient's recovery is practically assured. We are encouraged in this belief by the knowledge that the disease is self-limited and relapses are rare.

It is necessary to observe and record the amount of urine. Retention and suppression are frequent, the latter occurring late and the former early. Every specimen passed should be measured and tested for the presence of albumin at least, because the early appearance of albumin and its escape in the urine in large quantity may be regarded in a general way as an indication

of a severe attack. However large the quantity of albumin the physician may always feel encouraged if the patient pass from 500 to 1,000 cc. in twenty-four hours. In cases of moderate severity a trace of albumin is found by the end of the second or third day. In the mildest cases albumin may not be present at any time; or it may be found at one examination and absent at others. A distinct trace may be discovered by the end of the first day if the attack is a severe one.

Free elimination of the toxin early in the attack lessens the tendency to hemorrhage and modifies the subsequent course. Hence the great importance of instituting eliminative treatment at the earliest moment, and as all toxins are removed chiefly by the kidneys, it is essential to secure early and free secretion by these organs. In this probably lies the secret of the success of the alkaline treatment, which may also have some effect in neutralizing the poison if it be of an acid nature. The intestinal congestion and hemorrhages are of mechanical origin; they result from obstruction to the portal circulation through pressure upon the capillaries by the hepatic cells,which are swollen and fatty from the action of the toxin upon their protoplasm. Should the patient have a preëxisting lesion of the heart, liver, or kidneys, his chances of recovery are lessened; but the case is by no means hopeless, if treated early. If black vomit or intestinal hemorrhages supervene, the prognosis becomes very grave, but treatment should be continued to the last. By virtue of its stimulant, hæmostatic, and diuretic properties, oil of turpentine in 0.6 cc. (10 minim) doses deserves a trial, with applications of ice to the epigastrium, and alkaline waters and stimulants by the mouth or rectum. Thirty out of 36 cases brought to a hospital with black vomit are said to have been cured by inunctions with heated olive oil, and to-day many intelligent Spaniards in Cuba assert that they can cure yellow fever with olive oil and lime juice. It is well within the bounds of probability that olive oil applied by inunction may be of great value by reason of its nutritive properties. Like gelatine it possesses the power to serve the purpose of cell nutrition, and as it is a proteid sparer, it may keep the liver cells from attacking their own proteids during the period of their excessive functional activity. It could well be administered early in the fever either by the mouth or rectum, in the form of an emulsion with an equal quantity of lime water. Gelatine also is hæmostatic as well as nutritive and serves the same purpose.

For impending anuria it would be justifiable and advisable to give 1.0 gram (15 grains) of urea in the form of a hypodermic or rectal injection. It is non-poisonous in small doses and is directly indicated because it is the normal stimulant to the flow of urine, and it is of necessity wanting. The hot air bath should be as serviceable in ammonæmia as in uræmia.

For heart failure hypodermic injections of strychnine should be given.

The general treatment should be of the simplest and along the lines indicated. Careful and skillful nursing is indispensable. The patient should not be permitted to sit up or leave his bed until after several days of normal temperature. The value of the alkaline method is fully demonstrated by the results obtained by Touatre with Vichy water, and others with the Sternberg method, using mercuric chloride and sodium bicarbonate. These results are clearly to be attributed to the latter ingredient and not to the former. Among 374 cases treated by 10 physicians in the United States, Cuba, and Brazil, the mortality was only 7.3 per cent. The sodium salt is harmless and it is the normal alkaline base of the blood plasma.

CHAPTER XXVIII.

PLAGUE.

By W J. CALVERT, A.B., M.D.

Synonyms.—Pestis, pestilentia, febris, pestilentialis, pestis bubonica, clades inguinaria, glandularia, Beulenpest, Oriental plague, pali-plague, black death, plague, pestilenza, plaga, peste bubonica, tschuma, malignant polyadenitis.

Definition.—Plague is an acute infectious disease, running a rapid severe course, and often terminating fatally. It is generally characterized by extreme weakness, high fever, buboes, and severe general symptoms and is frequently accompanied by subcutaneous hemorrhages and pustules.

History.—In I. Samuel, Chapters v and vi, a fatal disease among field mice is recorded which also affected the Philistines. This was probably plague. Epidemic diseases occurring from this time to 200 B.C. are not described with sufficient accuracy to justify a diagnosis of bubonic plague. During this period several epidemics occurred which are quite accurately described by Rufus of Ephesus (about 100 B.C.) who also mentions epidemics in Libya, Egypt and Syria in his own time. The writings of Rufus are the first in which specific symptoms of plague are accurately given. Although it spread along the Mediterranean coast, no mention is made of the extent or duration of this, the first recorded pandemic. From this period to the Justinian age plagues are mentioned, but the accounts are too indefinite to differentiate bubonic plague from plague as the general term for any highly infectious disease. In 542 A. D. (Justinian age) plague started in lower Egypt and Pelusium and spread along the shores of the Mediterranean to Asia Minor and Europe. This is usually called "The Justinian Plague"; it lasted from fifty to sixty years, during which time the disease appeared again and again in the same locality. Wars, droughts, and famines, accompanied this pandemic, as in the time of Rufus. From this period to the fourteenth century the literature is again too indefinite to differentiate plague, although in all probability it played an important role in the several recorded epidemics.

It will be noted that the two previous pandemics began in Egypt and spread along the Mediterranean coast to Asia Minor and Europe. But in 1346 plague made its way from western Asia to Asia Minor, thence to Egypt and Europe. It must be supposed that during the previous epidemics the disease spread from Asia Minor to western Asia, perhaps farther into China, where epidemic centres were established which later gave rise to the plague. During this pandemic, plague spread over the then known world in the most virulent form, often depopulating entire villages. At this time it was first called the "black death," from the diffuse subcutaneous hemorrhages which in later epidemics have not been so frequent. The death-rate was high, Hecker estimating a total mortality of 25,000,000. During this pandemic, new infected centres were established from which epidemics sprang. Of

these Egypt in Africa, Turkey in Europe, and Syria in Asia, were the most important, whence throughout the following centuries numerous epidemics arose, many of which extended to neighboring countries. The last epidemic in Constantinople occurred in 1841; in Arabia in 1853, 1874, and 1879; in Tripoli in 1874; in Persia in 1863 to 1878; in Mesopotamia in 1866 and 1876; and in Astrakhan in 1878.

From 1879 to 1894 the world was practically free from plague, but in the latter year it was discovered in Hong Kong. Later it was found that this epidemic arose in or near Lientschau and Pakhoi, spread to Canton, thence to Hong Kong from which place it was carried to India, Japan, the Philippines, to numerous ports along the route to Europe, to South Africa, South America, Portugal, England, San Francisco, Mexico, and many other localities. In each pandemic plague travelled along the routes of commerce. All nations are susceptible, the lower classes suffering most severely. It is frequently recorded that domestic and wild animals suffer markedly from the disease. It has been noted that clothing and articles of merchandise have served to transport the disease, and that migrations of rats, etc., often precede or accompany its outbreak.

Bacteriology.—The *Bacillus pestis bubonicæ*, discovered by Kitasato, in 1894, is an encapsulated, non-motile, short, non-spore forming, aërobic organism, with rounded ends, measuring from 1 to 1.8 by 0.4 to 0.7μ. As seen in smears from the blood, lymphatic glands, and cultures, it occurs singly, in pairs end to end, and frequently in chains consisting of four to six bacilli; less frequently, especially when grown in liquid media, in very long chains. The capsule varies greatly, apparently influenced by culture media. Ordinarily the capsule of bacilli obtained from the blood or glands is about twice as thick as the organism; in artificial media it is usually not seen. In shape and size the organism varies, depending to some extent on the culture media. Those found in the blood are frequently plumper than those from the lymphatic glands, occasionally resembling cocci. On salt or mercuric chloride media various forms are seen, dumb bell, club-shaped, very wide long bars, etc. The large rod forms are more common in old cultures. The bacilli take all of the ordinary stains, decolorize in Gram's stain, and very frequently take a bi-polar stain leaving the central portion clear, giving a streptococcus-like picture. If the smear is first treated with absolute alcohol for one minute, dried, and quickly stained with dilute analine stain, a uniform bi-polar stain is obtained. Or if the Gram's stain is made and followed by dilute analine stain an equally good bi-polar stain is obtained.

Early in the course the bacilli are confined to the infected lymphatic glands or the tissues immediately surrounding them, but as the disease progresses the organisms enter the lymph channels and blood, and are later found in practically every fluid and organ of the body.

Cultural Characteristics.—The organism grows well in all ordinary media. Surface colonies twenty-four hours old are small, round, even-edged, almost transparent, with a slightly milky centre. The colonies are granular, slightly yellowish in color, and darker in centre than about edges, which are wavy or slightly indented. At forty-eight hours the colony is larger, more opaque, and of a milky color. On neutral plain agar-agar slants at the end of twenty-four hours a faint, translucent, slightly opalescent growth occurs with wavy smooth borders which are thicker than the central portion of the

streak. At the end of forty-eight hours, the streak is considerably larger than at twenty-four hours, and slightly more opaque, with scalloped edges. No further important changes are noted in older cultures except the development of beads over the surface of old smears, due to a local growth of the organism. When a portion of the culture is removed by a platinum wire a glutinous consistency is observed, the growth usually pulling out into long threads. On gelatine plates the superficial colonies are semi-translucent, with wavy edges. Deep colonies are round, whitish, and of regular outline. In stab cultures a whitish growth occurs along the stab, with here and there small colonies growing into the media. On the surface a slight growth may occur about the puncture. On blood serum a similar growth is seen, but slightly more opaque, with no change in media. On glycerine agar the growth is similar to growth on above-named media, but not so abundant. On acid potato the growth is sparse, slightly moist, and of a very faint yellow color with no change in the potato. In bouillon the most typical growth is seen, which occurs just under the surface and along the sides of the tube. From the surface the growth projects downward in light, flocculent, stalactite-like masses, which, on slightly shaking, settle to the bottom. The bouillon remains clear. No change is produced in litmus milk. In litmus glucose agar-agar, a slight reddening appears which gradually extends through the entire media; no gas is formed. In peptone solution no indol is formed. In hanging drop the organisms have an active Brownian motion, but are not motile. Plague bacillus is pathogenic for all domestic animals.

Virulence.—The virulence of the plague bacillus varies. A low virulence gives rise to pestis minor. These organisms may suddenly become highly virulent, and give rise to the severer types of plague. The virulence is gradually increased from low to a high degree by passing the organism through several animals. When high virulence is obtained it is easily maintained in cultures and by passage through animals. Cultures on artificial media retain virulence for months, perhaps years. Mixed infections do not necessarily reduce it. Cold temperatures have practically no effect; higher temperatures, 41° to 42°, reduce virulence.

Toxicity.—When young bouillon cultures are filtered the filtrate is not highly toxic, showing that the toxins are in combination with the bacteria; but when old cultures are filtered the filtrate is highly toxic, causing widespread hemorrhages, focal areas of necrosis, and fatty degeneration, enlarged spleen, and death. When the dose is not fatal a marasmus may follow, with marked loss of weight and hair, anæmia, and death after a number of weeks. At autopsy in monkeys the organs seem dry, shrunken, and of a light bronze green color. Sections show loss of nuclear material, and fatty degeneration.

Pathology.—The muscles are dark red in color, dry, and about a primary bubo may be hemorrhagic. The periosteum may be injected or hemorrhagic. The bone marrow is normal. The synovial membrane of joints near a primary bubo may be hyperæmic, rarely hemorrhagic, and the joints may contain a little light straw-colored fluid.

Skin.—The skin is usually dry and hot. Later in the disease profuse—often periodical—perspiration occurs, and occasionally terminal perspiration precedes death. In the several epidemics the degree of hemorrhages in the skin varies greatly. Hemorrhages are of two types, petechial and diffuse. Petechial hemorrhages occur on the face and upper extremities, but most frequently on the upper part of trunk. These hemorrhages affect

the skin only. The diffuse hemorrhages occur in the subcutaneous tissues and skin, are very large (four or five inches in diameter), irregular in shape, and of a dark bluish-black (often mottled) color. They occur most frequently on the trunk and upper extremities. When confluent an entire extremity or one side of the trunk may constitute one hemorrhage. In both types of hemorrhage bacilli are abundant. About scratches or insect bites a narrow rim of hyperæmia or hemorrhage usually occurs. Over large buboes the skin is often hyperæmic. Œdema of the skin is rare except over buboes, especially those associated with extensive œdema and in cases with marked nephritis.

Exanthemata resembling wheals frequently occur, often reminding one of mosquito bites. Abscesses may be formed and gangrene sometimes follows a suppurating bubo. Herpes is rarely found and has not been noted in plague pneumonia. Lymphangitis is rare, occurring both as primary and secondary to pustules and buboes, in which case the skin is thickened, œdematous, and hard, and on section shows bacilli, hemorrhage, hyperæmia, and infiltration with leukocytes and small cells.

Primary and Secondary Pustule.—Lodgment of bacilli in the capillaries of the skin may cause an infiltration of the tissues with leukocytes, small round cells, red blood cells, œdema, and an extensive invasion of bacilli. These cause an elevation of the epidermis from 2 to 5 or 6 mm., varying in extent from about ½ to 2 or 3 cm. in diameter. The edges are sharply raised without an areola. The elevated part is hard, and on section shows œdema, leukocytes, small round cells, red blood cells, and marked congestion. Within a few hours a small vesicle, which rapidly enlarges, forms in the centre of the elevated portion and, in a short time, the bleb covers the entire area. At first the fluid in the bleb is colorless, but soon becomes turbid; then pus forms which often contains blood. This fluid at first usually contains a pure culture of plague bacilli, leukocytes, small round cells, red blood cells, and detritus. The bleb is easily ruptured. When the fluid escapes, a red, swollen, hard base is seen, which soon becomes covered by a grayish or yellowish-gray scab. Often the scab is of a reddish or black color. On section the infiltration extends about 5 mm. into the subcutaneous tissue. Sections made in the earlier stages show infiltration, œdema, and bacilli. The cutis rapidly degenerates until entirely destroyed. All of the bloodvessels of the dermis are greatly dilated, the walls much thinned, and blood apparently coagulated. In some cases multiple small hemorrhages are noted. The vesicle enlarges by rupture of the stretched lower layer of cells along the circumference. The œdema and bacilli from a pustule may extend far beyond its edges into otherwise normal tissue, causing considerable swelling. A red line of œdematous hard tissue may extend from the pustule to the nearest lymphatic gland, which is enlarged. The pustule may either precede other symptoms or appear during the course of the disease. Multiple pustules sometimes occur, especially on the body. Those on the body are usually larger than those on the extremities. They are of no prognostic value.

Lymphatic System.—The lymphatic glands seem to be the elective seat of development. They may be classed as follows: Glands showing the most pathological changes, usually the first effected, are called primary buboes; glands in the chain or glands with the primary bubo, infected by the passage of bacilli through the lymphatic vessels, are called secondary buboes; and glands in distant portions of the body infected through the

blood are called tertiary buboes. The glands may be grouped as follows: Right and left femoral, including the femoral, inguinal, iliac, and lumbar glands; right and left axillary, including the epitrochlear, axillary, supra- and infraclavicular glands; and the right and left cervical, including the glands about the head, cervical, supra- and infraclavicular.

Primary Bubo.—This is characterized by periglandular œdema, infiltration, and glandular swelling. The œdema is pathognomonic for a primary bubo and dates from the beginning of the glandular swelling. At this time the areolar tissue between the muscles and tendons about the infected gland is slightly œdematous, of a lemon-yellow color, and soft. As the disease progresses the œdema rapidly extends in all directions, but confines itself entirely to the loose connective tissues. The skin covering the œdematous area is rarely, and the underlying muscles never, affected. In well-developed cases this œdematous tissue looks very much like a soft gelatinous mass, semi-translucent, and of a deep straw or lemon color. On section a thin, clear, straw-colored fluid escapes. This fluid contains a few pus cells, red blood corpuscles, and varying numbers of plague bacilli. The œdema varies from a very slight amount of fluid between the muscles to an amount sufficient to increase the size of the affected region. Œdema associated with a primary femoral bubo of one side may extend from the knee to the lower portion of the thorax anteriorly and posteriorly, in the retroperitoneal region as high as the diaphragm and occasionally beyond the median line. The degree of œdema does not depend on the size of primary bubo. Throughout this area the bloodvessels are distended, and punctate hemorrhages are often seen. The lymphatic vessels are usually distended and appear as whitish semi-translucent cords. These œdematous areas resist secondary infections longer than any other portion of the body. Consequently pure cultures of plague bacilli may frequently be obtained here when in all other portions of the body mixed cultures are found.

Periglandular Infiltration.—This, consisting of small round cells and few leukocytes associated with varying amounts of hemorrhage, is the second characteristic of a primary bubo. It begins in the first hours of glandular enlargement and rapidly progresses, often extending as much as an inch beyond the capsule of the gland. The infiltrated area is hard, more or less sharply outlined, on section moist, and usually intensely hemorrhagic. The massing of a group of glands into one hard body is caused by periglandular infiltration.

Bubo Proper.—The lymphatic gland begins to enlarge during the first few hours of the disease, progresses rapidly, and usually reaches its maximum size by the fourth day. The primary buboes are from 1 to 4 or 5 cm. in diameter and vary in shape. Primary buboes during the first five or six days are hard, simulating on palpation a solid rubber ball. During the first twenty-four to forty-eight hours they are isolated and freely movable, but later are firmly fixed by the periglandular infiltration. The capsule is usually greatly distended, often ruptured, and usually shows more or less hemorrhage, making it difficult to differentiate from periglandular infiltration. On section the glandular tissue bulges from pressure; the surface is moist and granular, and in absence of hemorrhage the color is grayish, frequently yellowish-gray. All degrees of hemorrhage are noted. Frequently the hemorrhages follow the lymph sinuses, producing red columns radiating from the hilus to the periphery of the gland. The

centre of the gland is soft but as a rule has not advanced to suppuration. After the fifth or sixth day pus may be found. The glandular substance is friable. Massive necrosis is caused by the rapid growth of bacilli and production of toxins. The bacilli evidently lodge in the peripheral lymph sinuses, where very large masses of bacteria quickly develop. In sections the masses of bacilli take a blue hæmatoxylin stain. A few leukocytes, red blood cells, and fragments of tissue may be seen. The lymphatic tissues show all stages of necrosis. The degenerating cells show a loss of nuclear material, swelling, small fat globules and granular material in the protoplasm of the cell which may or may not take a deep eosin stain. The degeneration is massive. The capsule is usually hemorrhagic and its layers may be widely separated and broken. The periglandular tissue is hemorrhagic, contains varying numbers of leukocytes, and shows a massive small-cell infiltration.

Secondary Buboes.—These differ from the primary buboes in that they lack periglandular œdema, infiltration, and the massive degeneration of the glandular substance, though the œdema arising from the primary bubo may surround them. All the lymph vessels connecting the primary and secondary buboes are greatly distended, appearing as smooth semi-translucent cords. The tissues immediately surrounding the secondary bubo are usually hemorrhagic. The degree of periglandular hemorrhage varies from a thin layer immediately next the capsule to a massive hemorrhage extending several inches into the tissues on either side of the gland, often uniting with similar hemorrhages from neighboring glands. The entire retroperitoneal tissue from Poupart's ligament to the diaphragm may present a massive hemorrhage along the chain of the iliac and lumbar glands. The bubo is usually hard, freely movable, and, if not hemorrhagic, grayish in color, and may be 3 to 5 cm. in diameter. On section the gland bulges, is usually dry, contains no pus in the centre, and usually presents long narrow hemorrhagic streaks converging at the hilus, with intermediary grayish or faintly yellowish-gray areas. The degree of interglandular hemorrhage varies greatly in the several buboes and also with the duration of the disease. Histologically, the secondary buboes are most interesting. From the onset of infection in the primary bubo, toxins, bacilli, and red blood cells, pass from it through the lymph vessels into the subcapsular lymph sinuses of the secondary bubo and gradually flow through the sinuses to the hilus of the gland. The red blood cells and bacilli lodge in varying numbers in the sinuses, producing a red hemorrhagic-like line through the gland, converging at its hilus. The bacilli continue to grow, forming colonies which in time may overshadow the characteristics of a secondary bubo by reproducing the same conditions as found in a primary bubo. This is rare save in closely located glands. The toxins at first act as a stimulus on the endothelial cells lining the lymph sinuses. In an early stage it is difficult to decide whether or not multiplication of these cells takes place. No karyokinetic figures have been seen, but the cells seem to be increased in number. A marked increase in size is noted. The nucleus takes a deep hæmatoxylin stain and the protoplasm the ordinary eosin stain. Some of the cells are giant in size and have assumed phagocytic function, shown by red blood cells, possibly by bacteria and fragments of tissue found in varying numbers in the protoplasm. The stimulating stage soon changes to a degenerative one; the nuclear material is gradually lost

and takes little or no stain, eventually leaving the nuclei as clear spaces in the protoplasm. The protoplasm has no constant staining quality, sometimes taking a deep eosin, again no eosin stain. Thus far changes have taken place only in and about the edges of the lymph sinus. The centre of the follicle and cords are still unaffected. Gradually the degeneration extends into the lymphatic structure of the follicle while the centre is yet normal. About this time toxins in the blood have become sufficiently strong to cause degeneration about the bloodvessels, and this now appears about the follicular artery. From this place the degeneration extends toward the periphery, leaving a horseshoe shaped band of relatively normal tissue between the degeneration about the lymph sinus and that about the follicular artery. The histological changes in the centre of the follicle will be described under tertiary buboes. When the follicular artery becomes degenerated, small intrafollicular hemorrhages occur, confined in the centre of the follicle. Occasionally these hemorrhagic areas unite, producing massive hemorrhage through the gland. The capsule is usually more or less hemorrhagic.

Tertiary Buboes.—These receive infection from the blood, and occur in all portions of the body. The glands are rarely larger than from 1 to 2 cm., freely movable, hard, and hyperæmic. On section the tissues are moist and hyperæmic. Hemorrhages, which rarely occur until late, are at first intrafollicular and later massive. The first changes occur in the centre of the follicle. A swelling of the endothelial cells lining the trabecular network appears, followed by cessation of lymphocytic production and gradual degeneration of the walls of the capillaries. Phagocytic action of the endothelial cells has not been observed in this region. Here the nuclear material is lost by karyolysis and the protoplasm takes little or no eosin stain. Any increase in blood pressure at this stage produces hemorrhage about the end of the follicular artery. The outer rim of the follicle and lymph sinus remains intact.

Frequency and Location of Buboes.—Russell records 2,641 primary buboes in 2,700 cases, or 97.8 per cent.; Wilm, in Hong Kong, 73 per cent. In the writer's series of 102 autopsies, primary buboes occurred in 101 or 99 per cent.

In the following table the distribution of buboes is given with respect to age and sex; adults over, children under, fifteen years.

	Inguinal.	Femoral.	Axillary.	Cervical.	Iliac.	General.	None.	Total.
Male Adult	16	21	6	1	3	1	1	49
Male Children	7	2	3	3	0	4	0	19
Female Adults	4	10	7	0	2	1	0	24
Female Children	4	3	1	1	0	0	0	9
Age and sex not recorded	..	..	..	..	..	1	..	1
Totals	31	36	17	5	5	7	1	102

A femoral primary bubo is prominent and hard. The œdema is easily recognized, often extending from the knee to the lower border of the thorax

anteriorly. When the œdema is well developed the bubo may on palpation apparently fluctuate, but on section is usually hard. The closely located inguinal glands may escape infection, none of them being more than slightly enlarged; or one gland in the group may be very large or the entire group may become affected and united by the periglandular infiltration into one solid mass. On section this mass has a very characteristic picture. The cut surface presents a deep-red, congested or intensely hemorrhagic tissue, dotted here and there with sections of the numerous lymphatic glands, which have a grayish or yellowish-gray color mixed with hemorrhagic areas not so deep in color as the red of the infiltrated periglandular tissue. Add to this the extensive œdema and one has a pathognomonic picture. The iliac glands may escape infection, or only one, or all, may become enlarged, hardened, and surrounded by hemorrhagic tissue or a massive hemorrhage throughout the retroperitoneal tissue. In the lumbar and pelvic glands the same condition may exist. Often owing to a backward flow of lymph, the iliac and inguinal glands of the opposite side may present pictures of secondary buboes. Owing to the proximity of the inguinal glands to the primary femoral bubo they may rapidly assume all its characteristics. Other glands involved are tertiary buboes.

A primary inguinal bubo presents a picture very similar to the femoral bubo. Usually one gland is much larger and the pathological lesions more advanced than in the remaining glands of the group. At first the large gland is freely movable, but within a few hours the periglandular infiltration includes all of the glands in one solid immovable mass, and the œdema is similar to that described above. The femoral and iliac glands of the same side, the lumbar, and often the iliacs, inguinal and femoral of the opposite side, are secondary buboes. All other affected glands are tertiary buboes. A primary iliac bubo presents a similar picture with œdema and periglandular infiltration. Here the inguinals—rarely, the femorals—of the same side, some or all of the remaining iliac, lumbar, and pelvic glands, and frequently the iliacs, inguinals and femoral of opposite side, are secondary buboes. Other glands affected are tertiary buboes.

A primary axillary bubo presents the prominence described, with œdema extending varying distances down the arm, over the back and chest as far downward as the lower border of the thorax, sometimes crossing the median line. Some or all of the glands in the axilla may be included in a solid mass. The remaining glands in the axilla, all of the glands in and under the pectoral muscles, about the clavicle, and into the thorax, and often many of the cervicals, may be enlarged and present the characteristics of secondary buboes. All other glands affected are tertiary buboes.

In primary cervical buboes the condition is similar to that above. The glands about the head, supra- and infraclavicular, and frequently a few glands on the opposite side, become secondary buboes. All other glands affected are tertiary buboes.

Development and Fate of Buboes.—No set order of development of a primary bubo exists. Generally speaking, three groups may be noted, as follows: (1) Early development of primary buboes. When the first general symptoms of the disease are noted there is one gland more prominent than the remaining glands of the group. Often this gland has not been noticed by the patient; in others the initial pain is severe. (2) The primary bubo begins to develop a few hours after the general symptoms. (3)

Twenty-four to forty-eight hours elapse before the glands begin to enlarge. After a gland begins to enlarge its progress is usually very rapid, reaching its maximum in from four to six days. Suppuration takes place during the second week, about the tenth day, and is caused by secondary infection. In a majority of fatal cases death occurs before suppuration takes place. In the event of recovery the primary buboes may not suppurate, resolution taking place; or suppuration may occur, often giving rise to gangrene which on account of lowered resistance is severe, and requires weeks, often months, to heal, or may be the immediate cause of death. The outcome of suppurating buboes is similar to other infections, but usually requires much more time for healing. Secondary buboes begin to develop within a few hours after onset of the primary bubo. When the primary bubo is one of a group, as an inguinal, it is often difficult to determine which is the primary and which the secondary bubo. Suppuration rarely occurs. During convalescence the glands return to normal size. Tertiary buboes appear quite early, following the entrance of toxins into the system. On account of the frequent occurrence of slightly enlarged glands it is difficult to determine when the enlargement first begins. Suppuration rarely occurs. In one case two glands simulating primary buboes were found, one in the axilla, the other in the groin. One of these was most probably a tertiary bubo.

Respiratory System.—The nasal mucous membrane is negative. The pharynx, larynx, and trachea are frequently hyperæmic, often having an intense dark violet-blue color, sometimes hemorrhagic. In the last stage of the disease œdema of the glottis may be present. Congestion and œdema of the lungs are common, and varying degrees of bronchitis and bronchopneumonia occur. The pleura, both visceral and parietal, frequently show punctate hemorrhages and often hydrops, especially late in the course. The lymphatic glands at the base of the lung and in the mediastinum are enlarged, presenting the characteristics of tertiary buboes.

Pneumonia.—The consolidation may be extensive, but is more frequently lobular. By the union of a number of lobules small consolidated areas are formed which on section are red and hard, and from the surface a thick yellowish fluid exudes. The lobule is filled with red blood cells, masses of bacteria, and but little serum. The alveolar walls are thickened and the vessels congested. Blood and masses of bacilli are found in the bronchi.

Circulatory System.— *Pericardium.*—The pericardial sac may contain a few centimeters of light straw-colored fluid. In the parietal layer the vessels are congested, and on the outer and inner surface numerous punctate or diffuse hemorrhages may be noted. On the visceral layer subpericardial hemorrhages, punctate or diffuse, are more common than on the parietal layer.

Heart.—The right heart is as a rule much distended, the left heart empty, the vessels distended, and the muscle flabby, showing parenchymatous and fatty degeneration. Often the intramuscular vessels are distended with leukocytes, and intramuscular hemorrhages occur. The heart valves and endocardium are normal save an occasional subendocardial hemorrhage. Very few lesions are to be found in the arteries. Periglandular infiltration may extend through the walls of a neighboring bloodvessel, causing massive hemorrhage and infiltration of the vessel walls, sometimes associated with a thrombus. Inflammation along a vas vasorum is sometimes noted. The capillaries are usually much distended, sometimes

thrombosed, often ruptured, causing extensive hemorrhages. Extreme congestion of the general venous system is one of the most striking conditions at autopsy. Extensive hemorrhages in the walls of veins near a primary bubo are frequently observed.

Spleen.—The spleen is usually enlarged, varying from normal to three or four times the original size. A typical plague spleen is firm, the capsule tense with perhaps a few subcapsular hemorrhages, and reddish-brown in color. On section the tissue bulges, the surface is dry or very slightly moist, the color red with a bluish-purple cast; the Malphigian corpuscles and trabeculæ are visible with frequent hemorrhages; the pulp is increased. The tissues are widely separated, with the small round cells and polymorphonuclear leukocytes increased, and some desquamation of endothelial cells lining the membranes. The fixed elements show varying degrees of cloudy swelling, fatty degeneration, and diminished amount of nuclear material. Intense congestion and frequent extensive hemorrhages are present. Focal areas of necrosis are sometimes observed. Plague bacilli are seen in masses, scattered through the tissues and intracelluiar.

Digestive Tract.—The mucous membrane of the mouth is usually dry, more or less hyperæmic, occasionally hemorrhagic, and frequently covered with a whitish or yellowish-white coat. The tongue is usually coated white; later, especially along the median line, the coat turns brown to brownish-black. The edges of the tongue are clean, red and œdematous. The papillæ are prominent. The tonsils may be enlarged, hyperæmic, coated white or yellowish-white, and occasionally show considerable enlargement, followed by pus formation and necrosis. In ordinary cases the sputum is negative, but when the disease has become systemic and in pneumonic cases bacilli may be found. The œsophagus is rarely affected, save by an occasional punctate hemorrhage. In the stomach no constant lesions are found. The mucous membrane is often hyperæmic and studded with punctate hemorrhage. Frequently there is an acute catarrhal gastritis with hypersecretion and more or less altered blood. The lymphatic structures may be swollen. The mucous membrane of the intestines may be hyperæmic, and hemorrhagic especially in the duodenum. The solitary follicles and Peyers' patches are swollen, but rarely show degenerative changes. Occasionally ulceration takes place. The mesenteric glands are usually enlarged, hyperæmic but rarely hemorrhagic. About the cæcum a chain of glands is frequently large enough to palpate. The peritoneum is usually dry. Occasionally a small quantity of light straw-colored fluid is present. Peritonitis sometimes occurs over an enlarged iliac gland. In the cases observed there was a thick yellowish-gray cheesy layer over the affected peritoneum.

Liver.—The liver is slightly enlarged and congested. Its surface presents more or less subcapsular hemorrhage, especially about the suspensary ligament, together with areas of fatty degeneration varying in size, and of a soft yellowish-white color. The lobules may be of a light color with the central vein prominent. A section shows cloudy swelling, areas of fatty degeneration and distention of bloodvessels. Hemorrhages rarely occur in the substance of the liver. Stained sections show varying degrees of parenchymatous degeneration and usually considerable fatty degeneration, which in areas completely obliterates the protoplasm of the cells and is most marked in the periphery of the lobule and in the area nearest the

arterial blood supply. At first the fat droplets are arranged in rows along the side of the cell nearest the capillary, making a very striking picture. The nuclei of the cells have lost a portion or all of their nuclear material. Focal areas of degeneration are found, containing broken-down cells, bacilli, and more or less blood.[1]

Pancreas.—The pancreas presents no changes save a large or small number of punctate hemorrhages.

Genito-urinary System.—The adrenals present no changes. The kidneys may show no changes; but varying amounts of subcapsular and punctate hemorrhages may be found, with varying degrees of parenchymatous and fatty degeneration. The pelvis is particularly prone to hemorrhage, either punctate or general. In the ureters and bladder hemorrhages sometimes occur. Cystitis is rare. Hyperæmia of the urethra has been observed. Severe uterine hemorrhage, especially at a period, is common, and abortion usually occurs in the pregnant. Œdema of the labia is not uncommon.

Urine.—The urine is usually diminished in quantity, of a high color, and of high specific gravity; contains a small amount of albumin, globulin, indican, and diminished chlorides, but no sugar. Epithelial cells, varying amounts of pus, and red blood cells with many granular and fatty casts are found. The blood in the urine depends more on the amount of hemorrhage along the urinary tract than on the degree of acute nephritis. Suppression of urine is common, especially in the later stages. Plague bacilli occur in the urine. One case of urethral discharge, thought to be gonorrhœal, was found to consist entirely of semen containing numerous pus cells with a pure culture of plague bacilli.

Nervous System.—Anatomical changes are rare. There are varying degrees of hyperæmia, with an occasional punctate hemorrhage in the meninges. Meningitis occasionally occurs. The nervous manifestations are largely functional, due to toxæmia and congestion.

Special Senses.—Rarely affections of the ear arise from extension of inflammation, from primary cervical buboes, and from hemorrhage. Conjunctivitis is common, and keratitis, iridocyclitis, and hypopyon occur, sometimes going on to panophthalmitis. Injection of the vessels of the conjunctiva is frequent.

Blood.—No change in the red blood cells is noted although a slight diminution in their number and hæmoglobin content has been mentioned. A polymorphonuclear leukocytosis begins with the disease, varying from 8,000 to 45,000 per cmm. The blood platelets are usually greatly increased. Plague bacilli enter the blood through the lymphatic vessels and by direct growth into a vessel through the tissues about a primary bubo. There is a progressive septicæmia, beginning a few hours after the onset and increasing until just before death, when the blood practically becomes a pure culture of bacilli. Clumps of bacilli are often observed in the peripheral circulation and many being too large to pass the capillaries, consequently form emboli and new colonies of bacilli, which grow through the walls of the vessel into the tissues, causing hemorrhage and frequently leading to thrombosis and pustules. In 31 fatal cases the bacilli were found as follows:—

[1] Icterus is not uncommon. It is probably due to pressure on the duct from enlarged lymphatic glands.

Within	24 hours before death	31 positive	100.00%;
Within	48 hours before death	15 positive	46.39%;
Within	72 hours before death	8 positive	25.80%;
Within	96 hours before death	3 positive	9.68%;
Within	120 hours before death	1 positive	3.22%.

In convalescence, bacilli may be found in the blood days after all traces of the disease have subsided—in 1 case after forty-five days.

Inoculation Experiments.—Practically all animals are susceptible to plague. Subcutaneous inoculation of a fatal dose produces a swelling about the seat of inoculation which on section shows marked œdema (pale yellow fluid exudes from the cut surface), varying degrees of hemorrhage, usually extensive, and infiltration of small round cells, few leukocytes, and varying numbers of red blood cells. The nearest lymphatic glands are enlarged, hyperæmic or hemorrhagic, hard, and on section show the changes found in a secondary bubo. Rarely is a primary bubo found, but if the clinical course is long, one may develop and go on to suppuration. Rats have been observed with large ulcers, most probably from plague buboes. All of the lymphatic glands are enlarged, hard, hyperæmic, and, on section, the changes incidental to tertiary buboes are noted. The blood shows a leukocytosis and plague bacilli varying according to the duration of the infection, but usually in large numbers. The spleen is enlarged, hard, often hemorrhagic, and on section the pulp is firm, brick-red in color, with structures visible. The liver is somewhat enlarged, often showing fatty degeneration. All of the organs, especially the heart, lungs, liver, and spleen, may show extensive hemorrhages. There is a remarkable similarity to the lesions found in human cadavers.

Plague Among Animals.—Widespread infections and migration of rats have frequently been noted just before an epidemic, when rats, dead of plague, may be found. Its origin among rats has not been determined, but it probably arises from infected material recently introduced into a district, or is propagated by mild cases among them. Rats with open ulcers from broken-down buboes are especially important factors in keeping the disease alive. Flies and fleas contract fatal plague; consequently the former may infect food and the latter transfer bacilli from place to place and their bite produce direct infection. Bacilli may remain virulent in the stomach of bedbugs for a number of days, but their bite is harmless unless the insect is mashed on the wound, when infection may take place. Ants harbor the bacilli for a number of days, and may carry infection from place to place, especially from cadavers to the surface of the ground.

Climatological Features.—Plague has been observed in frigid and temperate climates, but flourishes best in moderately warm, dry weather, such as is found in the tropics and sub-tropics from the end of winter to the rainy season, or usually from January to June. The maximum number of cases usually occurs before the hottest days. In these sections the onset and close of the epidemic is gradual, with isolated cases throughout the remaining months of the year. This seasonal periodicity is not absolutely constant, yet noticeably frequent. Elevation is of no importance, as the disease flourishes either at the sea level or in very high altitudes.

Portal of Entry.—Owing to the absence of local reaction about the seat of inoculation, it is always difficult and usually impossible to determine this. In inoculation experiments the lymphatic glands draining the inoculated

area are most affected. Consequently it is reasonable to infer that a primary bubo indicates in what area the infection occurred. It has been shown that primary buboes occur most frequently in the groin; next, in the axilla. Therefore the majority of infections occur through the skin of the extremities and trunk. Cases with primary pustule and lymphangitis offer no difficulty, but in others the areas immediately surrounding a scratch or wound are inflamed, making it impossible to tell through which lesion infection occurred. The probabilities are that infection may enter any abrasion or even a microscopic wound of the skin and mucous membranes. In children it is thought that infection occurs most often through abrasions in the buccal mucous membrane. Bacilli introduced into the stomach may or may not produce infection.

Direct Transmission.—In all well-advanced cases all of the secretions and excretions may contain the organisms in large numbers. Of special importance are the pus from buboes, excretions from pustules, vomitus, and the sputum in pneumonic cases. The sputum, sweat, urine, and fæces, in given cases, may be infected. Consequently the bedding, furniture, and room may become infected, and those in attendance are continually exposed to direct contact with infected material and may at any time become infected through abrasions, etc. Notwithstanding this, very few attendants in hospitals have contracted the disease. The cadaver contains many bacilli and consequently is a dangerous source of infection until disinfected or destroyed.

Indirect Transmission.—The viability of the organism and the relatively small number of bacilli necessary to produce infection are of importance in this connection. The organism is killed by direct sunlight in from two to four hours; protected from sunlight, even under unfavorable conditions, bacilli are capable of retaining life and virulence for an undetermined period. In cultures full virulence has been noted at fifteen months; on dried paper, at forty-five days; in cadavers, at forty-eight days; and in sputum, at seventy days. Exposure to intense cold does not necessarily kill the organism; 60° C. kills in an hour, and 80° C. in fifteen minutes. To the ordinary disinfectants the bacilli are very susceptible. Considering that even one organism may possibly produce infection, this longevity becomes important, especially in explaining a possible infection of rats and other vermin by old clothing, etc. It has not been shown that air and water carry the organism for any length of time. The long life of the organism and the probable infection through the skin make the hygienic condition of the individual, the home, and the section of a city or community, matters of the highest importance. The history of epidemics shows that plague thrives best among those who live in filth. The relative immunity of those living in hygienic surroundings is evidence of the important role of indirect transmission.

Spread of the Disease.—Convalescent patients, especially those with an old unhealed ulcer from a bubo, individuals who have been exposed to infection but have not yet developed the disease, migration of rats and other animals from district to district and especially on board ship, transportation of clothing and articles of merchandise, especially fabrics and raw materials, are the most important means of carrying the disease from district to district. Water and air are not good carriers of infection. Flies, fleas, and other insects may carry infection within limited areas.

When introduced into a new district the first few cases are separated by a considerable interval of time, and therefore attract little or no interest and too often pass undiagnosed. One or two years may elapse before an epidemic begins. The first few cases may establish infected centres from which the disease spreads. These cases do not always occur in the same house or in the same district. The second or third case may be found blocks away from the first known case. After the disease is fairly well established it does not necessarily go from house to house down a given street, but skips about from block to block. Only one member of a large household may suffer from the disease, and months may elapse before a second case occurs in the same house. But after the disease has become well established there develops what may be called infected centres or houses in which case after case is found. The annual duration of an epidemic is rarely longer than six months, during which time most of the cases occur within two or three months. Usually the daily number gradually increases up to the maximum, followed by a gradual decrease toward the end of the epidemic. A greater or less number of isolated cases occur during the remaining months of the year. The disease is probably kept alive during the interval by mild cases, infected rats and insects, and by infected materials, houses, etc.

Age, Sex, Race, and Occupation.—The young and old of all races are equally susceptible, yet the majority of cases occur between the ages of twenty and forty years, due probably to increased exposure. In childhood and after the age of fifty the numbers are proportionately small. The apparent immunity of some races living in infected districts is due to good hygienic conditions. Laborers at all trades are affected, but the freedom of workers in oil and water has been noted, probably due to the protection and cleansing of the skin by these substances.

Predisposing Factors.—These are fatigue, poor food, insufficient clothing, and the crowding of large numbers into filthy quarters.

Incubation Period.—From observations in isolation camps and accidental infections this has been found to vary from two to ten days. A few authors give fifteen days as the longest period.

Symptoms.—The clinical manifestations are very varied. The most important varieties are pestis minor, abortive or ambulatory plague, pestis bubonicæ or bubonic plague, septicæmic plague, pneumonic and intestinal plague.

General Symptomatology.—Sudden onset; rapid development of severe symptoms, such as high fever, severe prostration (often reaching a typhoid state within forty-eight hours), severe vomiting (often bloody), intense pain, headache, and pain about the buboes; severe nervous symptoms, such as restlessness, sleeplessness, delirium, epileptiform seizures, and coma followed by death within two to four days. The prostration is out of all proportion to the degree of fever and duration of the disease; there is a most peculiar facial expression, with the eyes bright and staring as if looking at a distant object; the conjunctivæ are injected, and nostrils dilated; the face expresses pain, fear, and anxiety; the respiration is hurried, and labored; the body is flexed. This picture, when once seen, cannot be forgotten.

Fever.—There is no characteristic fever-curve. Generally the symptoms are out of proportion to the degree of fever, which rarely exceeds 104° F.—occasionally 107° F. Its onset is not constant. In the first days a gradual rise is noted, reaching a maximum on the third or fourth day, after which

a gradual decline occurs. More often the onset is with a sudden rise as high as 103° or 104° F., after which there is in some cases continuous fever with daily morning remission and afternoon or evening rise. Frequently a remittent type occurs with morning remissions of from one and a half to two degrees. Occasionally a true intermittent type is present, the temperature falling to 96° or 97° F. A continuous curve for from two to three days may be followed by a drop of from two to three degrees or even to a subnormal temperature, to be followed by a rise above the highest temperature yet noted. In the second rise a remittent curve is usually present. Marked irregularity is perhaps the most constant feature. Sudden drops to normal or subnormal are not rare, and variations of from two to three degrees are common. Just before death there may be a drop of three or four degrees to or below normal, followed by a sudden rise of four or five degrees, and death. The fever continues from six days to four or five weeks, usually from six to ten days, and subsides, as a rule, by lysis to normal, or frequently to a subnormal temperature which may last several days. After several days of normal or subnormal temperature a second rise may occur. With suppuration the temperature is of the septic type, which rapidly subsides after drainage. With each succeeding glandular suppuration a similar rise occurs. In some cases even with marked buboes and general symptoms only a degree or two of fever may be noted. As a rule the cases with very high temperature are fatal; yet the degree of fever is not good prognostic evidence. Postmortem rise of temperature frequently occurs; 109° F. has been noted a few hours after death.

Pulse.—In no other infectious disease does the heart weakness manifest itself so early and so severely. Frequently at the end of the first, rarely later than the third day, pronounced symptoms of heart weakness are present. The pulse during the first few days is full, large, of moderate tension and often dicrotic; later it is small, weak, equal, regular, or often intermittent. The development of septicæmia has no influence on the pulse. The rate varies from about 120 to 180, and frequently late in the disease is much higher. Pulsus paradoxus has been noted. In very severe cases the pulse may become so weak and rapid that it is impossible to count it at the wrist. During convalescence a rapid, weak, and often intermittent pulse, is present for an indefinite time.

Duration.—Plague runs a most varied course. Fatal cases last from eighteen hours to fifteen days, but the majority terminate before the sixth day. Septicæmic plague is fatal in from eighteen hours to seven or eight days, usually before the fifth day. Pneumonic type is fatal in from two to seven or eight days, usually before the fifth. Bubonic type in the majority of cases is fatal before the sixth day. Usually death occurs before the bubo has had time to suppurate. Generally speaking, if the patient lives through the fifth day, his chances of recovery are good. Convalescence is often complicated by successive suppuration of a number of lymphatic glands and by severe heart weakness, often protracted for months.

Pestis Minor, Abortive, or Ambulatory Plague.—Pestis minor occurs during several months or a year previous to a general epidemic. The symptoms are light and very varied. One or more lymphatic glands, the inguinal most frequently, are swollen, more or less painful, and usually go on to resolution but rarely to suppuration. Few bacilli are found in the blood, while relatively large numbers are present in the fluid from a bubo. These organisms are not highly pathogenic. The general symptoms are slight head-

ache, general malaise, occasional vomiting, heart palpitation, slight diarrhœa or constipation, and low fever. The picture varies from simply an enlarged lymphatic gland to one with all the above symptoms in moderate degree. After a severe epidemic many cases of pestis minor occur, especially in infected centres. Some observers think that many so-called cases of pestis minor are climatic buboes. These must be differentiated from venereal buboes, dengue, and any of the infectious diseases with enlarged lymphatic glands.

Bubonic Plague.—The prodromal symptoms are general malaise, weakness, slight chills, pains in the head and limbs, sleeplessness, loss of appetite, vomiting, palpitation, and aching in the region of the future primary bubo. The onset is often accompanied by high fever, which reaches its height the first day, or more commonly, not until the second or third day, and is usually associated with slight initial chills. It is not uncommon for the chills to continue at short intervals throughout the course. The fever may rise gradually, reaching its maximum about the fourth or fifth day, and as a rule is very irregular, frequently being intermittent and usually showing a daily remission of from one to two degrees. In the usual favorable case fever lasts from seven or eight to ten days, when as a rule it subsides by lysis to, or a little below, normal for a number of days. After several days there may be, even in uncomplicated cases, a rise of one or more degrees for a short period. If suppuration occurs during the second week, a septic fever-curve may be present until the abscess is drained. In fatal cases the temperature may drop from 103° F. or 104° F. to or below normal within a few minutes, followed by a rapid rise to or above the previous temperature, and death; or the temperature may rise from 103° or 104° to 105° F. or even 107° F., to be followed by death. A dull aching pain in the region of the primary bubo sometimes precedes all other symptoms, but more often fever develops first. As the buboes develop rapidly, pain due to stretching of the tissues is severe, limited mostly to the region of the bubo. Pain continues until the active process has subsided, after which the patient is fairly comfortable until suppuration begins, during the second week. It is more frequent than resolution. Usually the tissues heal slowly, often requiring months, and frequently severe gangrene occurs. On account of the pain the patient assumes the position best suited to relieve pressure on the affected glands—this is, flexion of the leg on the trunk in primary inguinal bubo, the arm close to the trunk in primary axillary bubo, and the head to the affected side in primary cervical bubo. Internal glands may or may not be painful, but if large and numerous, severe pain is common. It is especially noted on pressure along the inguinal chain, and when the mesenteric glands are large, general pain over the abdomen is often severe. Suppuration of internal glands may lead to severe complications. The conjunctivæ are reddened, the pupils equal, often dilated, or more rarely contracted. In advanced cases the eyes are sunken and lusterless, with the corona somewhat clouded. In others the eyes are bright, staring, and may have an intense, anxious expression. The nostrils are widely dilated and move with each inspiration.

The mucous membranes may be normal or somewhat hyperæmic. The tongue is slightly swollen, covered with a white coat, with prominent papillæ, the edges clean, bright-red, and showing the imprint of the teeth. Later, especially in the centre, the coat turns to a dirty blackish-brown color. The buccal mucous membrane is red, œdematous, and occasionally covered

with a whitish coat. The pharynx is red, often bluish from congestion, and occasionally coated. The tonsils may be swollen and hyperæmic. Later in the disease the skin may show, over the face, trunk, and upper extremities, numerous small punctate, bright-red hemorrhages or, less seldom, over the trunk and upper extremities, diffuse, large, irregular, subcutaneous hemorrhages of a bluish-black color. During the first days the skin is dry and hot; later periodical or continuous profuse sweating may occur. Some authors ascribe a peculiar odor to plague patients. The pulse is rapid, small, of low tension, often dicrotic and rarely less than 100 and often 180. The respirations are rapid (40 to 60 per minute), superficial, and labored. At this time the patient with his anxious expression, quickened respiration, and flexed attitude, presents a pathognomonic picture which once seen suffices for a ready diagnosis. The heart is usually somewhat dilated, and may have soft systolic murmurs at the base. The lungs may show a few moist rales with harsh respiration, probably due to congestion and œdema. The spleen is enlarged, but rarely reaches more than about 1 cm. below the costal margin. The liver may often be felt. Diarrhœa or constipation may be present or alternate. The abdomen, unless the deep or mesenteric lymphatic glands are enlarged, is negative. The urine is diminished in quantity and occasionally retention may occur, more rarely anuria, especially for a few hours before death. The nervous symptoms are varied. Vomiting is common at onset and through the first few days. Headache may be severe and at the onset the degree of prostration may be phenomenal, the patient reaching a typhoid state within two or three days. Again the patient is restless, tossing about, excited even to delirium, talkative or crying by turns, even crazed, leaving the bed only to pass into epileptic seizures and fall on the floor, there to remain unconscious for a longer or shorter time. Awakening from this state, he may suffer intense pain, often relieved by passing into a benumbed or unconscious state. For a few hours before death coma is not uncommon. In other cases consciousness may be retained until the last. Owing probably to congestion, symptoms suggestive of meningitis may be noted.

Septicæmic or Fulminating Plague.—The onset is sudden, with high fever, prostration, and delirium. Prodromal symptoms may or may not be present. All of the symptoms are rapid and severe. All of the lymphatic glands are more or less enlarged and painful, but no primary bubo develops. The prostration is severe from the beginning and coma may develop early. Vomiting is often persistent and severe. Bloody diarrhœa is frequent. The pulse is rapid and of low tension. The spleen rapidly enlarges and is easily palpated. Death almost invariably results in from eighteen hours to three days after onset. These cases are often intensely hemorrhagic.

Pneumonic Plague.—Pneumonia occurs in two forms: first, lobar pneumonia caused by the diplococcus lanceolatus; and second, true plague pneumonia. Plague pneumonia appears either as primary, or secondary. In primary plague pneumonia prodromal symptoms are rare. The onset is usually sudden, with a rapid rise of fever, frequently accompanied by a severe chill or chills, and rapidly followed by severe headache, general body pains, vomiting, and severe prostration. The fever is high and usually irregular, occasionally intermittent; the pulse weak, of low tension, and rapid. The heart is weak, and, owing to a compensating emphysema, may present a diminished area of dulness. The spleen rapidly enlarges, is easily palpable, and forms one of the best differential signs. The respiration is rapid,

reaching 75 or over per minute. Cyanosis is usually marked. As a rule no primary buboes develop, but after the disease becomes systemic one or more may appear. Septicæmia develops early. The general symptoms described for bubonic plague, excepting buboes, may be noted in pneumonic plague. Plague pneumonia comes in two types, the bronchitic with limited bronchopneumonia, and a more extensive consolidation with less bronchitis. In both types cough is present. The bronchitic form presents a serous frothy sputum with more or less blood and often a pure culture of plague bacilli. The physical signs are rales, either fine crepitant or moist and piping, with harsh breath sounds, a slightly dull note, and no change in the vocal fremitus. When the consolidated areas increase the sputum contains more blood and dulness is more extensive. Often small dull areas may be outlined. In the more consolidated type vocal fremitus is increased; crepitant, moist, and piping rales are common; the breath sounds are rough and more tubular; and the consolidated areas larger, perhaps involving an entire lobe. The sputum is almost pure blood, bright-red and frothy, but is rarely tenacious. Dyspnœa and cyanosis are extreme. The intensely bloody sputum rarely occurs before the second or third day. Vomitus rich in blood and bloody diarrhœa are common. Pleural friction with pain is early and severe. The nervous manifestations are similar to bubonic plague. The duration of the disease varies from two to eight days, but usually death occurs within five days. Diagnosis is difficult and in the bronchitic type may be overlooked until autopsy. The glands at the base of the lungs are secondary buboes.

Secondary pneumonia develops from emboli or aspiration of infected material. Emboli arise from clumps of bacilli often found in the peripheral circulation, and from dislodgment of a portion or all of the small thrombi which commonly form in the capillaries. Mural thrombi in the veins near a primary bubo may give rise to emboli. Clinically the two forms cannot be differentiated and frequently are entirely overlooked. The embolic pneumonia may occur early in the course, the aspiration form usually toward the end, and regular lobar pneumonia in the last portion of the clinical picture. The embolic type usually shows numerous areas of consolidation throughout the lung, while the aspiration form is more often limited to the lower lobes. Clinically the increased respiration and cyanosis are of no diagnostic value, as both occur in non-pneumonic cases. Rales and small areas of dulness may lead to a diagnosis, especially if near the surface. A pleural friction rub, with severe pain, is not uncommon. If the consolidated areas assume large dimensions they may be recognized by the ordinary signs.

Intestinal Plague.—In this form the lymphatics of the intestines and mesenteric glands are most affected. The onset and general symptoms are as previously described, save the presence of marked vomiting of bloody material, bloody diarrhœa, and intense pains throughout the abdomen. Buboes are absent.

Sequelæ.—Various nervous affections, such as paralyses of various kinds, may follow plague. Inflammation may appear in the joints, middle ear, and especially in buboes one after another. Protracted heart weakness may continue for an indefinite period. Gangrene of the lung and protracted hemorrhage from the urinary passages are not uncommon. Suppuration of

internal buboes may lead to abscess formation in the peritoneal cavity or mediastinum.

Diagnosis.—During an epidemic this is very easy, especially the bubonic type; but before and after an epidemic, and especially before plague is known or suspected, a diagnosis is difficult and frequently the disease is not even suspected. Medical men in all seaport towns and in districts liable to infection should always have plague in mind. The first cases may present only a small swelling of a lymphatic gland with or without light general symptoms. Here the presence of plague bacilli in these glands and frequently in the blood is of great importance, and no time should be lost in puncturing the bubo with a hypodermic needle, and with the extracted fluid inoculating a mouse, rat, or guinea-pig, and making cultures. The condition of the inoculated animal and the cultures will give a positive diagnosis within a few days.

Climatic Buboes.—Light attacks with buboes and slight general symptoms must be differentiated from climatic buboes, which usually occur in the groin, are painful, and may go on to suppuration with fever. Their course is about one week. They occur sporadically or in light epidemic form. Bacteriologically the buboes and blood are negative.

Febrile Adenitis.—This occurs usually in children, sporadically or in epidemic forms. The glands of the neck, occasionally of the axillæ, are enlarged and painful. Fever reaching 103° to 104° F. may be present. Generally the disease is light and lasts but a few days. The glands and blood are negative bacteriologically.

Venereal Buboes.—Venereal buboes may simulate a light attack of plague. Here the history and bacteriological findings serve to differentiate.

Infectious Diseases.—Most of the infectious diseases may cause enlargement of the lymphatic glands. Here the clinical picture, severity of the attack, and bacteriological examination, distinguish the disease. Plague without buboes may simulate malaria, typhoid, and relapsing fever. Here the history is of importance, but the careful bacteriological examination should within a few hours suffice. In the tropics and subtropics dengue fever with enlarged lymphatic glands must be considered. Here the subsequent clinical picture, pain about the joints and muscles, the exanthem, and negative bacteriological findings are distinctive. Diphtheria with minor throat symptoms is easily differentiated. In cases with severe involvement of the mesenteric glands, especially those about the cæcum, and with a large tender iliac gland, appendicitis is suggested. Here a blood examination may be of value. An increase of blood platelets may suggest plague. The development of a bubo would determine the diagnosis. Isolated cases of plague pneumonia may go unnoticed. Here the sputum, rapid respiration, cyanosis, severe prostration, and enlarged spleen, should suggest a bacteriological examination. Skin lesions present no difficulty. A primary pustule may be differentiated from a malignant pustule by the bacteriological finding. In the absence of an epidemic a microscopic and bacteriological examination is the only possible means to a sure diagnosis. Even here some experience is often necessary. Fatal cases should go to autopsy, when the general venous engorgement, hemorrhagic character of all the organs, fatty liver, large hard spleen, enlarged lymphatic glands, and the presence of a bi-polar bacillus, suffice for a tentative diagnosis, until the organism has been identified. After this a positive diagnosis may be made.

Serum Diagnosis.—Agglutination of plague bacilli by serum from plague patients rarely occurs during the first week, more often in the second, and quite constantly in the third and fourth weeks; so that agglutination is of no value until late in convalescence.

Prognosis.—This depends on the general severity of the existing epidemic. The death-rate varies from 30 to 95 per cent. The general condition of the patient and type of plague are the most important factors. In order of severity the types are pneumonic, septicæmic, bubonic, and pestis minor. Prognostication is of little value during the course except in pestis minor. Clinically, the degree of dilatation of the heart and the strength of its beat are perhaps most trustworthy.

Treatment.—Symptomatic treatment is indicated. An initial purgative is good. Stimulants should be used, and if fever is high cold applications are of value. Some use is made of antipyretic drugs. Bichloride of mercury in large doses is recommended. For the headache, an ice-cap is preferable to drugs. For vomiting, cold applications to the epigastrium and ordinary remedies may be used. In severe hemorrhagic cases styptics are indicated. In violent or very restless cases hyoscine is of service. No treatment for the buboes will be effective until fluctuation suggests incision and drainage. Excision of buboes is of doubtful service and is often followed by serious results. In convalescence stimulants are valuable. All skin lesions should receive antiseptic treatment.

Prophylaxis—When plague is suspected an early diagnosis is all-important. Thereafter the disease should be handled in a general and special way. An efficient corps should be organized for the purpose of cleaning every nook and corner of the city or district and for reporting to one or more well equipped medical men every case of sickness. Each case of sickness should be visited as early as possible for diagnosis. Every case of plague should be removed to an isolated plague hospital and the inmates of the house should be placed in quarantine. General detention quarantine camps are questionable, for here many may be exposed for the first time to infection. Information should be given of the nature of plague. The town should be placarded with information regarding protection of the feet and legs; cleanliness of the house, clothing, person, and food; disposition of garbage, infected material, rats, etc. The general hearty coöperation of the public with the officials in charge of the plague work should be enlisted. At the plague hospital and detention camp should be men skilled in the diagnosis of plague to diminish as far as possible further exposure to infection. Infected houses or centres, clothing, furniture, etc., should be destroyed at the public expense. All articles capable of disinfection without injury should be disinfected. General disinfection of the houses and their contents, and destruction of rats, mice, insects, etc., should be effected as rapidly as possible. An early removal, followed by disinfection—or, better, destruction—of the dead is desirable.

Quarantine, to be of value, must be rigorous. Convalescents, infected materials (particularly fabrics), and rats (especially on board vessels), may carry infection. Effective quarantine measures would curtail commercial movements to what might be considered by business men an unwarrantable degree. Nevertheless, districts free from plague should insist on an absolute quarantine, since plague once introduced into a community is almost impossible to eradicate.

Prophylactic Inoculation.—Haffkine prepares a serum by the sterilization of a virulent bouillon culture, for one hour at 70° C. carbolic acid (0.5 per cent.) being added. The dose of this is from 2 to 3 cubic centimeters subcutaneously injected. A reaction follows with local swelling, more or less fever, headache, and general malaise. These symptoms rarely last longer than two days. Partial immunity appears in from seven to ten days and is said to last for from three to six months. Statistics indicate that these inoculations reduce the number and severity of infections.

Lustig's Protective Inoculations.—Lustig dissolves cultures on agar-agar in 1 per cent. solution of sodium hydrate and precipitates the glutinous or jelly-like solution with acetic or hydrochloric acid, then washes and dries the precipitate which contains the active principle and may be kept for an indefinite time. Three milligrams of this dissolved in 0.5 per cent. solution of sodium carbonate is an ordinary dose for an adult. A reaction follows the subcutaneous inoculation. With each succeeding inoculation this is lighter until finally no reaction occurs. When the horse is inoculated with sterile culture or Lustig's preparation, a serum is obtained which is protective and curative against plague in animals. Clinically, when fresh plague sera are used early and in large quantities, undoubted benefit results. The fever is lowered, pulse improved, and the degree of septicæmia lessened.

Vaccination.—Vaccination with attenuated cultures is not yet perfected.

CHAPTER XXIX.

BACILLARY DYSENTERY.[1]

By K. SHIGA, M. D.

Introduction.—Until recently it was customary to divide dysentery into three forms, epidemic, endemic, and sporadic; or to separate it, according to the clinical features, into two main groups, acute (catarrhal, fibrinous, or diphtheritic) and chronic or tropical dysentery. Since the discovery of the dysentery bacillus new light has been thrown upon the disease, and now many authors agree to divide dysentery into two forms, bacillary and amœbic.

Bacillary dysentery is an infectious disease produced by the *B. dysenteriæ*. Pathologically it produces catarrhal and diphtheritic inflammation, with the formation of necrotic ulcers in the intestine. Clinically it is characterized by frequent slimy and bloody stools accompanied by tormina and tenesmus.

Historical.—Dysentery has been a well-known disease since ancient times, and has existed in all lands from the earliest ages. It is mentioned in the Papyrus Ebers (1600 B.C.). The dysenteric affections have prevailed in large or small epidemics, often in pandemics in severe form. Always a constant companion of war, it has been more fatal to armies than powder and shot. Notwithstanding its frequent occurrence and high mortality, the etiology of the disease was not determined until recently, and only in the last half of the nineteenth century have the investigations into the cause of the disease arrived at satisfactory results.

In 1875 Lösch, in St. Petersburg, by his thorough investigations first proved the association of amœbæ with one type of the disease. Eight years later a variety of amœba was found by Koch in Egypt in bloody mucous discharges, in the intestinal membrane, and in the liver of dysentery patients, which is to be regarded on the basis of animal experiments as the etiological factor in Egyptian dysentery. Soon after this the disease was also thoroughly investigated by Kartulis. Osler was the first in the United States to demonstrate the amœbæ in a liver abscess. Subsequently these findings were verified by many observers but in spite of severe endeavor, all workers failed to find amœbæ in the stools or in the bowels of patients with epidemic dysentery, which was more destructive than the tropical or endemic dysentery. There is a large literature on the question of the etiological bacteria in this form of dysentery. Of these, the reports of Chantemesse and Widal, Kruse and Pasquale, Arnaud, and Celli and Fiocca are most noteworthy. Chantemesse and Widal (1888) found in the walls of the large bowel, in the mesenteric glands, and in the spleen, at autopsy, and in the stools of five persons suffering from tropical dysentery, a bacillus which they con-

[1] Dr. Shiga wrote this article in English himself. As few changes as possible were made, it being thought better to leave all expressions, the meaning of which was clear, without alteration.—Editor.

sidered specific and probably the cause of the disease. According to Widal, his bacillus may be identical with the *B. dysenteriæ*, which is now accepted as the true cause of bacillary dysentery. Arnaud examined 60 cases of dysentery in tropical climates and concluded that a sort of *B. coli communis*, or a pathogenic variety very much resembling it biologically, was to be regarded as the cause. Celli and Fiocca studied dysentery in the tropics and reported that it was caused by a specific variety of the colon bacillus, namely, *B. coli dysentericus*. This organism secrets a powerful toxin, capable of producing typical dysentery when given by the mouth or rectum, or injected subcutaneously into the connective tissue of animals. His bacillus is entirely different from *B. dysenteriæ* in its coagulation of milk and in the production of gas on glucose media. Notwithstanding this he would identify his bacillus with the *B. dysenteriæ*.

In 1898, Shiga[1] found the *B. dysenteriæ* in the epidemic dysentery in Japan and this organism showed marked agglutination when mixed with the serum of patients. In 1900, Flexner, Strong, and Musgrave studied cases of dysentery in the Philippines and isolated a bacillus which corresponds in all marked points with that of Shiga. Almost simultaneously with the papers of Flexner, Kruse (1900) published his investigation on an epidemic of dysentery in Germany and found a bacillus corresponding with that of Shiga. Thereafter the bacillus was found and confirmed by v. Drigalski in the epidemic among the troops at Döberitz, and by Pfuhl and Schmiedecke in the dysentery which broke out among the soldiers after their return to Germany from the China expedition. Furthermore, the bacillus was found and confirmed by Spronck in Holland, Vedder and Duval in the eastern part of the United States, Müller in Austria, Rosenthal in Moscow, Vaillard and Dopter in Vincennes, Jürgens in Prussia, Deycke in Constantinople, and Castellani in Ceylon, each in a native epidemic. In cases of summer diarrhœa in infants in the United States the dysentery bacillus was found by Duval and Basset, by Knox, and Wollstein. In 1903 the study of this disease was specially undertaken by Flexner and Holt with their assistants. By this investigation it became apparent that the dysentery bacillus can also cause infantile diarrhœa in both summer and winter. In Japan, Ohno, an assistant in Kitasato's Institute, has found and confirmed the presence of the bacillus in summer and winter diarrhœa. It was found in the stools of the patients and in the bowel wall and mesenteric glands at autopsy. In the Russo-Japanese war the bacillus was found in dysentery in Manchuria, among the Russian troops at Port Arthur, and in Korea.

Bacillus Dysenteriæ.—Morphology.—Dysenteric bacilli are small plump rods with rounded ends, very similar to colon bacilli. They are usually single, but occasionlly occur in pairs. They are not motile,[2] and no flagella can be demonstrated. There is no spore formation. The bacillus stains readily with the ordinary analine dyes, but is decolorized by Gram's method.

Cultural Characters.—The bacillus grows well on the usual culture media. Gelatine is not liquified, nor indol produced (see Type of Dysentery Bacilli).

[1] Shiga, "Ueber den Erreger der Dysenterie (Vorl Mitteil.)" *Centr. f. Bakt.*, 1898; "Ueber den Dysenteriebacillus," *ibid.*, 1898.

[2] In the first investigations I described the bacillus as being slightly motile. Kruse has described his bacillus as non-motile, and now his view is accepted universally.

Gelatine Plates.—Deep colonies are round or oval and possess sharp borders. Surface colonies are often, but not constantly, leaf-like in appearance, like the colonies of typhoid bacilli.

Agar Culture.—Like the typhoid bacillus they show less growth than the colon bacillus. After twenty-four hours in the incubator they form small, thin colonies which are round and have a moist appearance when viewed obliquely. After several days they become thicker, of a grayish-white color, and show thread formation. The agar culture is remarkable for a sperm-like odor.

Glucose-agar shows grayish-white growth along the entire line of inoculation but no gas formation.

Bouillon shows even clouding with sedimentation, but after standing for a time the upper part becomes clearer.

Litmus milk gives weak acid formation after one to three days in the incubator and after five to seven days an alkaline reaction and a gradual increase in the blue color of the culture.

Potato.—The development is different according to the reaction of potato used. If the potato is acid, the growth is not perceptible by the naked eye. It is, however, apparent and brownish or white in color if the potato is cooked in a soda or salt solution, and is alkaline or neutral in reaction.

Involution Forms.—When *B. dysenteriæ* is cultivated upon agar which contains a large percentage of salt, various involution forms are seen. Upon 5 per cent. NaCl-agar such forms are especially prominent, and appear in very irregular shapes. Hata showed that involution forms become specific and more prominent upon $\frac{3}{4}$ per cent. calcium-agar.

Animal Experiments.—The injection of a small quantity of dysentery bacillus culture into the peritoneal cavity of guinea-pigs causes a mucous, often a bloody diarrhœa; the animal dies in a few days. At autopsy the peritoneum is found markedly injected, and in the peritoneal cavity there is an abundant bloody exudation. The contents of the intestine are slimy and in the walls of the cæcum severe hyperæmia and hemorrhages are often obvious. Among animals this result is most marked in rabbits. The injection of even a small quantity of bacillus causes severe catarrh and hemorrhages upon the serous membrane and the walls of the bowels, with paralysis of the limbs and death of the rabbit after some days. Recently the author succeeded in causing a dysenteric lesion in the walls of the bowels (cæcum), just as in a human body, by injecting a small quantity of dysenteric bacilli. The mucous membrane of the bowels presented severe œdema, hyperæmia, hemorrhage and gangrenous degeneration. The microscopic changes were similar to those of human dysentery.

The Soluble Toxin.—The action of the dysentery bacillus toxin is very characteristic, and rabbits are very sensitive to it. When 0.1 cc. or less of the filtrate of a seven-days' bouillon culture is injected intravenously it causes the death of a rabbit in twenty-four hours; at autopsy remarkable hyperæmia and hemorrhages upon the serous membranes and the walls of bowel are visible, just as with a living culture. Rosenthal, Todd, Kraus, and Doerr, report the same result. A similar action of the toxin is also produced with the filtrate of a twenty-four-hour agar culture heated at 60° C. for one hour and diluted with normal saline solution (Neisser and Shiga). The toxin which Conradi has obtained with autolysis is also identical with the toxin above mentioned. The soluble toxin consists of two components: (1) a nerve

toxin which produces paralyses in the limbs and urinary bladder with severe hemorrhages in the cord, and (2) enteric toxin which causes the dysenteric changes in the bowels (especially the cæcum).

These toxins, obtained by different methods, are qualitatively identical; the animal experiment shows this accurately, and we can also prove it by the action with immune serum (Todd, Rosenthal). Heating at 70° C. for an hour has no influence upon this toxin; even its exposure to 80° C. does not seem to destroy it entirely, although it is affected slightly at 75° C.

The Types of Bacillus Dysenteriæ.—It was Kruse who first paid attention to the difference of serum reaction between the bacillus of Shiga-Kruse and that of Flexner (Manila type). In this investigation he described a so-called "pseudodysenteric bacillus" which he found in the stools of insane patients suffering from a form of dysentery and also in material from autopsies. This organism he could not distinguish morphologically nor culturally from the dysenteric bacillus, but it differed in the serum reactions. Spronck isolated an organism from patients suffering from dysenteric symptoms in Utrecht. This bacillus differs from the Shiga-Kruse organism in the agglutination reaction, and apparently belongs to the same group as Kruse's pseudodysentery bacillus; but its etiological significance is probably established.

The committee for the investigation of *B. dysenteriæ* (Koch, Pfuhl, Schmiedecke, v. Drigalski, and Jürgens) studied carefully the Shiga, Kruse, Flexner, and Döberitz bacilli, and found that the Flexner type differs from the others in its agglutination reaction with the patient's serum. Shiga,[1] compared the action of the immune serum on the Shiga and Kruse organism and found that they are identical from the agglutination and bactericidal standpoints. He showed, further, that there is a difference in receptor apparatus between the bacillus of Shiga-Kruse and that of Flexner. When the immune serum is saturated with a Shiga culture, all the agglutins and pro-agglutinoids for Kruse's organism are absorbed by the bacilli; and when these are removed with centrifugalization, the serum is no longer able to agglutinate fresh additions of Shiga-Kruse bacilli, while its limit for the Flexner bacillus is only slightly changed, or *vice versa*. This experiment was later confirmed by Eisenberg.

Martini and Lentz[2] published an article on the differentiation of dysentery bacilli by means of agglutination. They showed with immune sera that the Manila bacillus of Flexner and Strong differs from that of Shiga and Kruse. Lentz[3] could show this differentiation also on the mannite agar culture. The principal difference was that the Shiga-Kruse bacilli did not affect mannite (non-acid form) while the Flexner and Strong cultures fermented mannite (acid form) giving rise to a distinct acid reaction in the medium.

Hiss and Russel[4] described a bacillus (B. "Y") from a case of fatal diarrhœa in a child, and found that this bacillus differed from the Kruse cultures in its ability to ferment mannite.[5] Hiss distinguished at least

[1] Shiga: "Weitere Studien über den Dysenteriebac." *Zeitschr. f. Hyg.*, 1902.

[2] Martini and Lentz: "Ueber die Differ. der Ruhrbaz mittels der Agglut.," *Zeitschr. f. Hyg.*, 1902.

[3] Lentz: "Vergleich. Cultur. Untersüber die Ruhrbaz.," etc., *ibid.*, 1902.

[4] Hiss and Russel: "Study of a Bacillus Resembling the Bacillus of Shiga," *The Medical News*, 1903.

[5] This observation was made independently of Lentz's work.

three groups among the bacilli isolated from dysentery or diarrhœa cases, cultivating these in the medium of mannite, dextrose, maltose saccharose and dextrin. One group represented by the Shiga-Kruse culture fermenting monosaccharides only; one of the Hiss and Russel culture fermenting monosaccharides and mannite; and finally a group represented by the Flexner culture fermenting monosaccharides, mannite, maltose, saccharose, and dextrin.

Gay[1] studied the types of dysentery bacilli in relation to the bacteriolysis and preventive power of sera. He concluded that "the dysentery bacilli fall into two types, according to certain cultural and agglutinating reactions; but these reactions are not absolute, but relative, and serve to give the bacilli the characters of a closely related group of organisms. Bacteriolytic differences serve to distinguish the two types of dysentery bacilli, now recognized as sharply as the other tests hitherto employed."

Park, Collins, and Goodwin[2] divide the dysentery bacilli into three types: (1) No production of indol; does not ferment mannite, maltose, or saccharose (Shiga bacillus), (2) ferments mannite, but does not split maltose or saccharose, produces indol, and, (3) produces indol and actively ferments mannite, also acts energetically upon pure maltose and feebly upon saccharose. The occurrence of the different types of dysentery bacilli is confirmed by many other authors (Park and Dunham, Wollstein, Vaillard and Dopter, Doerr, Hetsch, Jürgens, Leiner, and others).

From these observations it is obvious that there are many different types of dysentery bacilli, and each of these can be the etiological factor in dysentery (Flexner, Strong, Jürgens, Spronck, and others). As to the classification of these bacilli; Hiss[3] studied this question and divided them according to their fermentative action upon monosaccharide (dextrose), disaccharides (maltose and saccharose), polysaccharide (dextrin), and the mannite, with which the agglutination reaction and the absorption tests agree. The groups are divided as follows: The first group ferments only monosaccharide (Shiga, Kruse, New Haven bacillus). The second group ferments monosaccharide and mannite ("Y," Ferra, Seal Harbor bacillus). The third group ferments monosaccharide, saccharose and mannite (Strong's bacillus). The fourth group ferments monosaccharide, mannite, maltose, saccharose, and dextrin (Harris, Gray, Baltimore, Wollstein bacillus). In the epidemic of dysentery in Japan, 1904, we collected at the institute in Tokio many types of dysentery bacilli from several parts of Japan and studied their differences. We have found a new type which ferments dextrose, mannite, saccharose, maltose and dextrin as the fourth group of Hiss, but differs from it in returning to an alkaline reaction after four or six days. The agglutination test of this type showed a wide difference from the others, so that this bacillus should be placed in a new type. The bacteriolytic as well as the agglutinative action of immune sera of our four types differ also from each other. The classification is given in the following table:

[1] Gay: "The Types of B. Dysenteriæ in Relation to Bacteriolysis and Serum Therapy," etc., *University of Pennsylvania Medical Bulletin*, 1903.

[2] Park, Collins, and Goodwin: "The Dysentery Bacillus Group and the Varieties," etc., *Journal of Medical Research*, vol. xi, No. 2, 1904.

[3] Hiss: "On Fermentative and Agglutinative Characters of Bacilli of the 'Dysentery Group,'" The *Journal of Medical Research*, vol. xiii, No. 1, 1904.

Dysentery bacilli.	Dextrose	Mannite	Saccharose	Maltose	Dextrin	Lactose	Indol reaction
I type.	+	−	−	−	−	−	−
II "	+	+	−	−	−	−	+[1]
III "	+	+	+	−	−	−	+
IV "	+	+	+	+	+	−	+
V "	+	+	+	+	+	−	+

+ shows positive fermentation and − negative.

It is to be noted that the high virulent toxin action on rabbits exists only in the first type (Shiga type) but not in the others.

As to the relation of those five types of dysentery bacilli to the pathology, symptomatology, and epidemiology, we know only a little. Flexner and Holt[2] make no difference in the clinical features of the summer diarrhœas of infants caused by the mannite fermenting and non-fermenting organisms. It is important to note that the Shiga bacillus and Flexner-Harris bacillus (the mannite fermenting organism) often exist in the same patient. Thus Gay and Duval[3] reported 3 cases in acute adult dysentery, Hastings[4] 2 cases, and Duval and Shorer[5] 6 cases in the diarrhœal diseases of infancy. It must also be mentioned that the frequency of occurrence of each type differs according to year, season, place, and epidemic.

Thus in the epidemic of dysentery in Tokio, 1904, we confirmed the presence of bacilli belonging to the first type in but a few cases, but those belonging to the third and fifth type in a large number, while a greater number of cases in Kobe in Japan, in Manchuria, Korea, and among the Russian troops in Port Arthur, was caused by the first type and only a few cases were caused by the other types (mannite fermenting bacilli).

Infection and Epidemiology.—The most important source of infection is the individual suffering from dysentery. The organisms occur in the stools in innumerable numbers, and through carelessness the clothes of the patient and also other articles are soiled and the bacilli thus carried from one person to another. In this way we find contact infection in a large number of cases in every dysentery epidemic (Shiga, Kruse, Köttgen, Wolfberg and others).

Then, too, the dysentery bacilli are often carried into rivers and other water supplies with the dejecta and cause infection through the drinking-water. Duprey's water-borne epidemic, which occurred at Grenada Island, in 1901, is the best example. In a village called Momma-Mura, at Nobechi, in Japan, in 1900, a dysentery epidemic broke out in houses situated near each other. It was proved that the well, used by all the households suffering from the disease, was infected with the dysentery bacillus. We have also an interesting example of river-water infection in Japan. There is a village called Mitake-Mura in the district Miyagi-Ken, through which a river flows. Fishing and swimming are prohibited in it because of fish breeding. In the late summer of 1899, the prohibition having been removed,

[1] The indol reaction of this group has only a trace in 1 per cent. peptone water; but in 2 per cent. peptone water, after long cultivation (five to seven days), the indol reaction is apparently visible.

[2] *Studies from the Rockefeller Institute*, vol. ii, 1904.

[3] Gay and Duval: *University of Pennsylvania Medical Bulletin*, 1902, vol. xvi.

[4 5] *Studies from the Rockefeller Institute*, vol. ii, 1904.

the men of the village were very glad to be allowed to fish and swim once more in the river. However, after four or five days an epidemic of dysentery broke out with 10 patients on the first day, and increasing numbers daily afterward. There were in all 413 cases, of which 115 were boys under ten years of age. After investigation it was found that there was an epidemic of dysentery in a village higher up the river, and the water had been soiled with the infected clothes.

The transportation and handling of milk or other kinds of foods may also be a cause of an epidemic of dysentery, and, indeed, sometimes a common bath-house may be a cause of infection. We had such an instance in Kobe in Japan. It is probable that the fly has some part in the transmission of the disease. It is easy to understand that a fly having settled on the dejecta of a dysentery patient can carry away the germs of the disease and deposit them directly upon food or even in the mouth.

As in other epidemic diseases, dysentery prevails especially among people who live in unhygienic surroundings. It always accompanies war. In the Japanese-Chinese war (1894-1895) we had 10,681 patients (of whom 1157 died, or 12.7 per cent.), the number of patients being about 10 per cent. of all diseases, and, indeed, 3½ times more than the wounded.

The severity of the epidemics differs, as is shown by the mortality. In the whole of Japan this varies every year between 22 and 26 per cent. of cases.[1] According to Kruse,[2] the mortality in Germany is 10 per cent., in Russia it amounts to 17.5 to 12.2 per cent (Rosenthal.)[3] According to Manson,[4] the mortality from dysentery among Europeans in India ranges from 3 to 22 per cent., among the natives about 36 to 40 per cent.

Age and Season.—Young men from twenty to thirty years of age very often suffered from dysentery, as in typhoid fever perhaps because of frequent exposure. Epidemics prevail from the early summer (June or July) until the late autumn (October). Through winter there are only a few cases and in some parts of the country it disappears entirely, although only to reappear in the next year. We can therefore suppose that the dysentery bacilli exist through the winter in the human subject, who either seems perfectly healthy, or suffers only from slight diarrhœa. We really have such cases. Ohno has found the bacillus in the stools of an apparently healthy man living near a household in which there was an epidemic of winter diarrhœa. Wollstein[5] found the bacillus at autopsy in 3 infants who had no symptoms of dysentery or summer diarrhœa, the bowels showing only a slight catarrh. She aptly says at the conclusion of her report: "*B. dysenteriæ* may be present in the intestinal mucosa in cases of a very mild catarrhal inflammation of the colon, either as a terminal infection or as the remains of a previously active infection when clinical manifestations do not warrant the diagnosis of dysentery." Conradi[6] found the dysentery bacillus in the apparently normal dejecta of 5 healthy infants aged two and one-half to eleven years, whose sisters and parents at that time

[1] Shiga: *Deutsch. med. Woch.*, 1901.
[2] Kruse: *Centr. für allgem. Gesundh.*, 1900.
[3] Rosenthal: *Deutsch. med. Woch.*, 1904, No. 19.
[4] Sir Manson's *Tropical Diseases*, 1903.
[5] Wollstein: "The Dysentery Bacillus in Relation on the Normal Intestine of Infants." *Studies from the Rockefeller Institute*, 1904, vol. ii.
[6] Conradi: Ueber eine Contact epid. von Ruhr," etc. *Festschr. zum 60 ten Geburtstage von R. Koch*, 1903.

suffered from dysentery. During an epidemic of summer diarrhœa, Duval and Shorer[1] succeeded in isolating a few colonies of the Flexner-Harris bacillus (mannite fermenting bacillus) from the stools of two infants who were in perfect health.

It is interesting to know how long after convalescence the dysentery bacillus exists in the stools of patients. We can, *a priori*, suppose that, as in typhoid, the bacillus can be found long after recovery. It was lately stated by Momose in Japan that the dysentery bacillus disappears from the stools of convalescents after thirteen to fifteen days. But there are exceptions, for the bacillus may be found in the stools a month after without any intestinal disturbance. V. Drigalski reported relapses occurring at intervals and also instances of relapse in soldiers after their arrival in Germany from China. Lentz reports the case of a soldier, who, after recovery from dysentery, left the Döberitz regiment and became the cause of a dysentery epidemic after his return to his native village. According to the results of investigations undertaken by Ohno with myself, the persistence of bacilli in the stools depends upon the severity of the attack; the lighter this is the sooner the bacilli disappear, even after five days; but the more severe the attack the longer the bacilli persist, even to the nineteenth day after convalescence.

Patients either with no symptoms or slight ones only, and convalescents who have been discharged from the hospital but have dysentery bacilli in their stools, are often the cause of fresh epidemics in places where dysentery has not been for a long time.

Pathological Anatomy.—The lesions of epidemic dysentery are those of a diphtheritic catarrh of the bowels. The large bowel is usually the seat of the disease, but it affects the cæcum and part of the ileum not infrequently. The dysentery bacilli remain in the folds of the intestine and multiply under favorable conditions, among which may be mentioned constipation and intestinal disturbances. The mucous membrane reacts by inflammation which may be catarrhal, hemorrhagic, or diphtheritic, according to the stage and grade of the process. The diphtheritic infiltrated mucous membrane becomes necrotic, and thus ulcers are produced. The elevated parts of the mucous membrane, the folds, are most affected, and from these the process spreads later to the surrounding parts. The process is more severe in the parts which are more intensely irritated by the contents of the bowel, as seen at the flexures and in the rectum.

In the beginning of the catarrhal period of the disease, the surface of the mucous membrane has a grayish-red, velvet-like appearance. The mucous membrane becomes red and swollen in consequence of hyperæmia and catarrhal œdema. This is succeeded in the second period by necrosis of the epithelium, which is noticable macroscopically by the presence of flecks, which microscopically are nothing but the groups of epithelial cells, the nuclei of which are hardly stained. Gradually the necrosis proceeds in the deeper parts and the whole wall of the bowel now appears thickened. The lymph follicles of the mucous membrane become necrotic and purulent and with the sloughing of these as the third period of the disease appears, comes the formation of ulcers. In contradistinction to the undermined ulcers of amœbic dysentery, which increase deep in the mucous membrane, the ulcers in epidemic dysentery are accompanied usually with only the damage

[1] *Studies from Rockefeller Institute*, 1904, vol. ii,

of flat layers with irregular borders. The formation of the ulcers proceeds deep in the submucous and to the muscular layer, often leaving the muscular layer bare. The border of the ulcers is reddened, swollen, and infiltrated.

In the small intestine the mucous surface throughout may be normal, or more commonly the mucosa in the lower portion of the ileum is more or less reddened. In the period of so-called "enterodysentery" the ileum presents in general the same reddened, hemorrhagic appearance, is covered with a necrotic mucous layer and œdematous swelling as in the large bowel. The writer observed a case in which the small intestine was involved for nearly one meter above the iliocæcal valve and was entirely ulcerated and diphtheritic; the wall was as thick as the colon. The Peyer's patches are only moderately swollen or not at all; the solitary follicles may be swollen, raised and hemorrhagic. Osler remarked that in very acute forms, as in children, the picture is that of an acute follicular colitis. According to Howland,[1] the summer diarrhœa of infants in the United States is accompanied anatomically with various features, either with pseudomembranous or follicular catarrh, superficial necrosis, and ulceration in the mucous membrane, or even only slight erosion.

The peritoneum is also inflamed, and adhesions frequently exist. Ecchymosis is present on the serous membranes in severe cases. If the lesions of the small intestine or cæcum are suitably localized the corresponding mesenteric glands will become swollen and show slight hyperæmia, as in typhoid fever. Strong remarks that the group running toward the head of the pancreas seems particularly likely to be involved. The kidneys often show injection of the surface vessels and cloudy swelling. The spleen is not enlarged and shows no constant pathological change. The liver generally is neither hyperæmic nor swollen.

The dysentery bacillus probably does not enter the general circulation. That such is the case is apparent from the fact that dysentery is never complicated by roseola, pneumonia, osteomyelitis, or the so-called infectious spleen, as in typhoid fever. The case of septicæmia mentioned by Rosenthal, in which he found the dysentery bacillus in the heart blood, in pericardial hemorrhages, and in the spleen and mesenteric glands at autopsy only nine hours after death, is an exception. Markwald reported an interesting case relating to the blood infection of the fœtus. The mother had dysentery and aborted in the sixth month. The child died in a few hours. According to the author it had lesions suggestive of the early stages of dysentery, and the dysentery bacillus was found in its intestinal contents and also in small numbers in the heart's blood. Parotitis is occasionally seen as a complication, but its connection with the dysentery bacillus is not clear, inasmuch as it may result from a secondary infection by other organisms present in the mouth.[2]

The pathological changes in the intestine predominate in the mucosa and submucosa. In the catarrhal period we can observe microscopically the bloodvessels of the mucosa and submucosa dilated and filled with blood. In the dilated lymph spaces groups of leukocytes are visible. In the early periods the mucous membrane shows a coagulation necrosis with a fibrinous exudate and polymorphous cells. The submucosa is usually very much thickened. In certain parts of the submucosa, especially in the deeper

[1] *Studies from the Rockefeller Institute*, 1904, vol. ii.
[2] Shiga: *Deutsch. med. Wochenschr*, 1901, No. 48.

layers, there is a marked cell infiltration. The borders of the ulcers are infiltrated and the surrounding tissue, also, shows a small cell infiltration.

Numerous bacteria are found in the inflamed mucous membrane and are especially numerous in the necrotic portions. They are usually bacilli, but cocci are also found. In the deeper layers the bacilli are found in small numbers; but in the glands, between the gland cells, and in the glandular stroma, they are very numerous. Cocci are not found in these locations. In the submucosa, and often in the muscularis, the cell infiltration is accompanied by the presence of numerous bacilli. Those seen in the deeper layers of the intestinal wall cannot be differentiated morphologically as the *B. dysenteriæ*, but transplantations from these regions show the presence of that organism in pure culture.[1]

General Symptoms.—Bacillary dysentery is a disease usually of acute course. The incubation period is generally two or three days, but cases are reported in which it was from three to eight days. In a case reported by Lemoine, in which infection took place by the rectum from the use of a chamber containing dysenteric stools, the incubation was twenty-four hours. Cases of infection in the laboratory which were observed by Flexner, Strong, and Kruse, showed an incubation of twenty-four to forty-eight hours. In the epidemic caused by river water which occurred in a village in Japan the incubation was in most cases from four to five days.

Dysentery begins with diarrhœa and colic. At the onset the stools are of the ordinary diarrhœal character, or contain only small quantities of mucus. There is lack of appetite, weakness, and a feeling of pressure over the abdomen. Abdominal pains and tenesmus soon develop. As a rule, on the second or third day the stools become slimy and bloody in character, and very soon only pure mucus and blood are passed. The stools then have a typical appearance and a characteristic spermic odor. The quantity passed is small, usually only a half or one ounce. In severe cases the stools contain pus and rarely shreds of mucous membrane. When the bowel wall is widely affected and hyperæmia and inflammation exist, the "meat-water" stools may be passed. The dirty-brown stools are often mixed with gangrenous tissue.

Tenesmus is very marked, and so intense that the rectum frequently becomes prolapsed and fæcal incontinence supervenes. This disagreeable symptom occurs very often in infants.

The body temperature in severe cases rises generally to between 101° and 102° F.; not infrequently it exceeds 104° F. The urine is decreased in amount and tenesmus of bladder is caused.

The quantity of food ingested is diminished, the appetite often disappearing entirely. The tongue is moist and somewhat coated in slight attacks. In the gangrenous or "typhoid" dysentery, when the outlook is serious, there is a thick and dirty-brown coating to the tongue, which may be dry. In chronic dysentery the tongue seems atrophic, reddened, and bleeds easily. Thirst is rarely present in the lighter cases, but in severe ones it is usually marked. The patient grows weak very rapidly, not only from the want of food, and restlessness, but also as a consequence of the action of the toxin of the dysentery bacilli. Nausea and vomiting are also often associated. When the patient has retching but vomits nothing there is usually epigastric pain.

[1]Shiga: *Deutsch. med. Woch.*, 1901, No. 43.

The pulse is in most cases accelerated and in serious cases small and irregular. The abdomen is usually somewhat excavated and tender on pressure. The infiltrated intestine can be plainly felt through the abdominal wall, this giving the patient great pain. The sensorium is usually clear. The patient complains often of headache and sleeplessness. Delirium is present rarely and only as a terminal symptom.

Death occurs in serious cases usually after two to three weeks, unless there is some complication to hasten it.

The general symptoms of dysentery are due to the absorption of the toxins of the bacilli (endotoxin) in the body. In mild cases fever and general indisposition are absent, but they are never-failing symptoms in serious cases and those of middle grade. That the general symptoms are not so prominent as in typhoid fever is to be ascribed to the localization of the lesions. If lesions are present in the upper portion of the large intestine or in the small intestine, various intoxication symptoms appear, such as fever, headache, general malaise, muscular pains, epigastric oppression, sleeplessness, numbness, stupor, delirium, etc. If such symptoms are present it was customary to speak of "typhoid dysentery." The rapid emaciation observed is not to be exclusively ascribed to the diarrhœa and inanition, but is partly due to the intoxication. Ecchymoses are frequently present upon the epigastrium, chest, or inner surface of the upper and lower extremities, and in the later and severe stages of the disease.

As above mentioned, the intestinal lesions are principally located in the flexures of the colon. This is without doubt due to the fact that the mucous membrane in such locations is extremely susceptible to mechanical irritation and hence is especially suitable for the development of dysenteric bacilli. The involvement of the lower portion of the small intestine is usually secondary, but it is very probable that primary lesions in this location do occur. As in typhoid fever, the usual seat of the lesion in dysentery in the small intestine is the lower portion of the ileum. The ileocæcal valve is frequently affected, being ulcerated and sometimes entirely destroyed. As a rule the cæcum and ileocæcal valve are extensively diseased; the intestines above are progressively less and less involved. The histological changes in the small intestine are entirely similar to those described above for the large intestine. Many mesenteric glands are enlarged and merely hyperæmic, as in typhoid fever. Following the healing of the ulcers the lumen of the intestine is narrowed by cicatrization. This is namely "enterodysentery,"[1] which is thus named in order to separate it from "colodysentery," in which the lesions are localized in the large intestine and rectum.

The symptoms of enterodysentery are somewhat different from those of colodysentery. In the former, tenesmus is absent and the stools are not so frequent, but very voluminous; mucus and blood are closely mixed with the stools. No incontinence of fæces is present. Tenesmus is always a sign that the rectum is involved. In distinction from colodysentery, in enterodysentery the toxic symptoms which have been described above in connection with the so-called typhoid dysentery are very prominent. The prognosis in enterodysentery is always serious. It is evident that the differentiation between entero- and colodysentery is very important on pathological, clinical, therapeutic, and prognostic grounds.

Shiga: *Deut. med. Woch.*, 1901.

As already mentioned, in most instances the disease begins in the lower portion of the large intestine (sigmoid flexure and rectum) and gradually extends upward. There is, however, no doubt that the lesions can arise primarily in various portions of the small and large intestine, when suitable conditions are present for the multiplication of the bacilli and inoculation of the intestinal wall. When the primary lesion is situated in the ileum or upper portion of the large intestine and the process advances downward, it is called "descending dysentery" in contradistinction to "ascending dysentery," in which the reverse is the case and the primary lesion is situated in the lower portion of the large intestine, the process extending upward. The latter form is that usually met with. The author has noted a case of descending dysentery in a nurse, who was carefully observed from the onset, in consequence of her presence in the hospital. The lower portion of the ileum and the cæcum were first attacked. She had, therefore, from the beginning a higher temperature and complained especially of general weakness and headache. The patient was also restless and complained of sleeplessness. She had pain in the umbilical region and this was especially marked on pressure in the right iliac fossa. The ascending, transverse and descending colon was entirely free at the beginning. Slimy stools, with large amounts of blood, were passed about nine times during the first day. No tenesmus was present. After a time the disease proceeded gradually to the lower portion of the bowel, from the cæcum to the colon ascendens, transversus and at the end to the upper part of the colon descendens; the progress of the disease was accurately proved by the pains on pressure. Under treatment with calomel and serum injections, the process was stopped and after three weeks she was in normal health.

Chronic Dysentery.—Under this term is included the dysenteric disease in which the catarrhal symptoms have disappeared. With the fæces are mixed mucus and material secreted from the areas of ulceration, and excreted only attached to the fæces without being mixed through them. The process is very chronic and extensive, and we may have stricture of the bowel. The condition is, in the writer's opinion, only a subsequent disease, in which we cannot find the dysenteric bacillus or amœbæ.

Summer Diarrhœa in Infants.—The so-called summer diarrhœa in infants, which prevails in the United States every summer in large cities, especially in the warm parts of the country, was studied in 1902, first by Duval and Basset, later by Knox and Wollstein. They found the dysentery bacillus in the stools of patients. In 1903 the investigation was undertaken by many workers under the leadership of Flexner and Holt, and it confirmed the view that the majority of the cases of summer diarrhœa are caused by the *B. dysenteriæ*—the most by acid bacilli, in a few cases by non-acid bacilli (namely non-fermenting mannite bacilli). This disease is characterized by much mucus and generally blood in the stools, usually with fever, which is always high, and by marked general prostration. We meet very rarely the severe acute intestinal intoxication called "cholera infantum" with its sudden violent onset, protracted vomiting, high temperature, frequent serous discharges, great prostration, early collapse and often early death.

In Japan, especially in the southern parts, there are also acute infantile diarrhœas, called "ekiri," in the season of dysentery epidemics. Ohno proved in an epidemic in Tokio, that the disease was nothing but dysentery

in most cases, in which, however, the intoxication symptoms are very serious and found the dysentery bacilli in the stools of the patients in 65 per cent. The clinical features were almost similar to those prevailing in the United States.

The Course.—The duration of the disease is four to eight days in the light cases and three to six weeks in the serious ones. According to the author's experience the duration, on an average, was forty days under medicinal treatment and twenty-five days under serum treatment. The onset in the light cases is tolerably prompt; in severe cases, on the contrary, it is rather gradual over some weeks. In the chronic dysentery the secretion of matter and mucus is obstinate, and continues for a long period after the other symptoms have disappeared.

Relapse is seen also not infrequently; but in most of these cases, the disease is of a chronic nature and characterized by irregularity in the movements of the bowels, or light diarrhœa which becomes serious again, after various indiscretions such as overexertion.

Complication and Sequelæ.—*Parotitis* occurs often in severe cases, and also in moderate cases which run a chronic course. It is usually bilateral and appears during the third to the fifth week of the disease. Unilateral parotitis is rarely seen. Among 436 cases of dysentery the author saw only 8 cases of parotitis.[1] The dysentery bacillus was never found in the pus and tissues removed. Perhaps parotitis may be caused by other bacteria which penetrate from the mouth into the gland.

Ascites is often seen in debilitated patients or during convalescence, and is frequently combined with general dropsy. *Peritonitis* occurs somewhat often in the course of dysentery. *Beriberi* (*Kakke*) is also often observed as a complication in Japan. The prognosis is not good.

Abscess.—The author has seen only 2 cases during convalescence. In the first the upper portion of the rectus abdominalis, and in the second case the gluteal region, was affected. No one has ever observed abscess of the liver in bacillary dysentery.

Inflammation of articulations and tendon sheaths has occurred, which is to be regarded as the general result of toxæmia.

Lately Iwasaki, in Japan, reported a case of mixed infection of dysentery and typhoid fever, from the stools of which he cultivated the bacillus of dysentery and also that of typhoid. At autopsy typhoid ulcers were found at the lower part of the ileum and dysenteric ulcers in the whole of the rectum. Woodward mentions that the same combination was exceedingly frequent during the American Civil War. On the contrary, in ordinary practice this is very rare. Eight similar cases are reported by the Eastern Asia Expedition Corps. Because in tropical and subtropical regions both bacillary and amœbic dysentery are simultaneously present, we can *a priori* expect mixed infections of these diseases. V. Drigalski found the dysentery bacillus and also dysentery amœbæ in the dejecta of a patient who returned to Germany from China.

As rare complications of dysentery Markwald reports acute conjunctivitis, iridocyclitis, and prostatitis.

Diagnosis.—The diagnosis of dysentery is usually very easy, especially in epidemics. We must regard the characteristics of the stools, colic, tormina, tenesmus, resistance over or swelling of the large bowel, and pain

[1]Shiga: *Deutsch. med. Woch.*, 1901.

on pressure. We must remember that tenesmus is not a constant symptom because it exists only when the rectum is affected. The diagnosis of the abortive form of dysentery, which occurs often in winter or in the beginning of epidemics, is very difficult. Similarly, too, the diagnosis of entero-dysentery, or the so-called typhoid dysentery, is not easy. The conditions necessary for a definite diagnosis of dysentery are the positive agglutination reactions of the dysentery bacillus with the blood serum of the patient, and the isolation of the bacillus from the dejecta of the patient or from the organs of the dead.

Furthermore in the differential diagnosis attention must be paid to exclude carcinoma, polypi, and syphilis of the rectum, hemorrhoids and mercury poisoning. Amœbic dysentery must be differentiated etiologically, clinically, and anatomically, from bacillary dysentery. The following are the most important points in this:

1. Amœbic dysentery usually runs a chronic course.
2. In the amœbic form no dysentery bacilli can be found, except in the mixed infections of both amœbic and bacillary dysentery.
3. In amœbic dysentery toxic symptoms, such as high fever, general malaise, anorexia, rapid emaciation, or various nervous symptoms, are not observed.
4. In bacillary dysentery liver abscess is never present; it is a very frequent complication of amœbic dysentery.
5. The anatomical processes are also different. According to Kartulis and Kruse, the edges of the ulcers are peculiarly undermined in amœbic dysentery, while in bacillary dysentery this is never the case and the ulcers are situated on the surface of the folds of the mucous membrane.

Bacteriological Diagnosis.—In the bacteriological diagnosis the agglutination of dysentery bacilli with the blood serum of the patient, and the isolation of the bacillus from the dejecta, are required, with the following methods:

1. In general, a positive agglutination reaction is first present in dysentery during the second or third week of the disease, and during convalescence reaches its highest point, then gradually subsiding in intensity.[1] Occasionally it appears for the first time at the end of the sixth week. This reaction, however, is of little value in the diagnosis of dysentery, as so often it is first present too late and it is not constant. The reaction is usually also weaker than in typhoid fever. When the reaction occurs in a dilution of 1 to 20, it must be regarded as positive. Usually the reaction occurs in 1 to 20 to 50 dilution. Occasionally in mild dysentery the reaction is negative (1 to 10). The higher reaction, however, occurs not rarely (Shiga, Kruse, Rosenthal and others). According to Kruse, the reaction in dysentery is higher and in one case was positive at 1 to 1,000 dilution.[2] It seems to me that the reaction is usually higher in the infections caused by the mannite fermenting bacilli than in those caused by the bacillus of type I.[3]

[1] Shiga: *Deutsch. med. Woch.*, 1901.

[2] It must not be forgotten that the agglutinating power of a bacillus varies according to its race and the media upon which it is grown. Furthermore it must be mentioned that the maximum limit of agglutination varies according to the technique employed and the individual judgment of the observer.

[3] In some cases caused by the bacilli of type IV, Ohno found a high agglutination above 1 to 3,000. Duval reported also some similar cases caused by the so-called Duval bacillus.

The problem of the reaction in dysentery is not simple, because there are many types of dysentery bacilli, each of which can be highly agglutinated only by its own blood serum, even among the mannite fermenting types. The reaction can be also more or less used in estimating the prognosis of dysentery. According to my own observation, two prognostic facts may be deduced: (1) If the agglutination reaction quickly increases in intensity the prognosis is favorable. (2) The prognosis is unfavorable or doubtful (unless the disease is very chronic) if the intensity of the agglutination reaction does not increase, or, if at all, but slightly.[1]

2. *Isolation of dysentery bacilli* from the stools is only of limited application, because it is rarely successful in mild cases and during the first days of the disease. If, however, the localization of the process is in the lower portion of the large intestine, the *B. dysenteriæ* is present early in the stools, and is more easily isolated than the typhoid bacillus in typhoid fever. The dysentery bacilli are especially numerous in slimy dejecta mixed with fresh blood. For the isolation of dysentery bacilli from the stools it is best to take up first some slimy flecks, and after a short washing in sterilized water to put the material directly into the culture medium, as follows:

1. Superficial smearing upon the agar plate with a right-angled bent glass rod (v. Drigalski), or the glass stopper of a glass bottle (Ohno), both sterilized.

2. The superficial smearing upon v. Drigalski's litmus-lactose-agar[2] or Endo's fuchsin agar.[3]

The colonies of dysentery bacilli on the agar plates are smaller, lighter in color and more transparent than those of colon bacilli. The colonies on the Drigalski's plate can be examined in sixteen hours. The colon bacillus and the group of saprophytes make the medium acid by the decomposing of lactose, and the colonies become red in color in its neighborhood, while the dysentery bacillus causes no change in color because of not decomposing lactose. The colony of the latter is round, with sharp contours, almost as clearly transparent as dew-drops and about 1 mm. in diameter. On Endo's medium the dysentery bacillus makes a colorless or only light-red thin colony while that of the colon bacillus seems thick and deep-red. The further examination of the colonies proceeds with the agglutination phenomenon done by the hanging drop examination of slight dilutions of dysentery serum (most conveniently done with rabbit serum of high agglutination power). When this proves positive, the glucose agar culture and cultivation in milk are done. If no gas is produced and the milk is not coagulated, while the bacillus has no mobility, then the microörganism may be regarded as *B. dysenteriæ*. But to know the type of bacillus it is necessary to test the fermentation upon carbohydrates and the agglutination phenomenon with specific sera of every type.

Prognosis.—In the consideration of this, the localization of the lesions in the intestines must be known. If they are limited to the sigmoid flexure or rectum the prognosis is favorable; but if the transverse and ascending colon or the small intestine is involved the prognosis must be given very

[1] Shiga: *Deutsch. med. Woch.*, 1901.

[2] V. Drigalski and Conradi: *Zeitschr. f. Hyg. n. Infect. Kr.*, Bd. 39, 1902; Lentz, "Dysenterie" *Kolle and Wassermann's Handbuch der path., Microörg.*

[3] Endo: Ueber ein Verfahren zum Nachweis der Typhusbac. *Centr. f. Bact.*, 1903, Bd. 35, No. 1.

cautiously. In short, the higher the lesions are situated in the intestine the more marked are the intoxication symptoms and the more unfavorable is the prognosis. For this reason the first principle in the treatment of the disease is to limit the upward extension of the process as far as possible. Nervous symptoms and other toxic manifestations set in when the upper portion of the large intestine or the small intestine becomes involved. They constitute a very unfavorable sign, and patients showing them usually die.

As regards sex, the mortality among females is larger than among males, as the following table shows:

LOCATION.	MALE.		FEMALE.	
	Number of cases.	Mortality.	Number of cases.	Mortality.
Province Niegata (1897)	4312	21.5%	2362	22.3%
" Shizuoka (1899)	1319	23.2%	1141	25.3%
Tokio City Hospital (1900–1904)	931	15.4%	708	26.8%

It is remarkable that adults of twenty to thirty years of age are most often affected with dysentery. In infants under the age of five years and adults above fifty years the prognosis is unfavorable. The mortality of epidemic dysentery is small in the beginning of the epidemic (May, June, and July), and increases gradually, reaching the maximum at the end of the epidemic (in November and December). In winter we have a higher mortality caused by the influence of the season upon the disease and from the chronic course.

Treatment.—The treatment of dysentery involves: (1) Keeping the patients absolutely at rest and having them warmly covered; (2) inhibiting the stimulating factor in the intestine; (3) attending carefully to the diet; and (4) proceeding with the etiological treatment.

The diagnosis of dysentery being established, the patient should at once be sent to bed. This of itself has a marked influence on the bowel. Repose must be as nearly complete as possible. Besides, it is necessary to cover the patient warmly, and a woolen abdominal bandage is advisable.

The indication of rest we further endeavor to meet by stopping all solid food. The diet should be taken in small quantities at a time—a little every two or three hours. The tongue is a fair index to the sort of food most likely to suit the patient. When this is coated, indicating gastric catarrh, small quantities of thin chicken broth, egg albumin, thin barley or rice water are taken better than milk; when the tongue is or has become clean, then milk—pure, diluted with barley or rice water, or peptonized—is the best diet. In Japan we are accustomed to give rice gruel, eggs and fish (the so-called "sashimi"). Alcoholic liquors are not recommended in dysentery, but in case of collapse a small quantity of white wine may be given with advantage. The food must be given neither hot nor cold, as food when either too hot or too cold is apt to excite peristalsis and cause colic and straining.

Most authors are agreed that calomel has the best effect in the beginning of the disease. The writer uses it to clear out the bowels and remove the

infectious material, in order to hinder the extension of the disease upward; 0.5 to 0.8 gm. (8 to 12 gr.) of calomel may be given once or twice, or 10 to 20 cc. (℥ iij to v) of castor oil, which is to be given but once. In other cases one can give 0.5 gm. calomel, and after an interval of one or two hours, 10 to 15 cc. of castor oil. Plehn[1] recommends giving the castor oil (15 cc. [℥ss]) first, and beginning the next morning, hourly, for twelve hours, a tablet containing 0.03 gm. (gr. ½) of calomel and 0.36 gm. (gr. vj) of calomel in all. The same is done during the next two days, being omitted in the night.

In addition, the patient is ordered simple acid lemonade or tartaric acid lemonade or alkaline waters. Enemata of 1 per cent. saline or soda solution are also recommended to remove the stimulating and infectious contents of the bowel and to assist the regeneration process in the mucous membrane. By the use of enemata tenesmus is diminished and the patient feels the disease less disturbing. Enemata of silver nitrate, tannin or quinine solutions and the like are not recommended in acute dysentery. The experiment of Berther is to be noted. He used enemata of methylene blue solution both in tropical and bacillary dysentery with good results. According to Berther, the effect of methylene blue is based upon the following points: (1) Its bactericidal action is not absolute, but it diminishes the virulence exceedingly. (2) It decreases reflex action by its analgesic effect, and excites the secretion of bile remarkably, which acts as a disinfectant and the secretion of which is very much diminished in dysentery. (3) Vomiting is also influenced favorably by giving the remedy internally. This remedy may be given as irrigations (½ to 1 liter with 0.1 to 0.2 gm. of methylene blue). These are conveniently given after a movement with the patient in the knee chest position. Internally we give doses of 0.1 to 0.2 gm. According to Berther, there are no ill effects found in using it.

For the tenesmus, suppositories of cocaine, opium, or extract of belladonna may be used. For the hemorrhage from the bowels, an ice-bag is applied over the abdomen, and opium is given internally. The patient must be absolutely at rest. Injections of ice-water or of 0.1 per cent. ferric chloride solution are recommended. For collapse the subcutaneous injection of physiological saline solution is effective.

Other so-called dysentery remedies, which are well known and used generally, such as ipecacuanha, pomegranate bark, antidysenteric pills, and others, are entirely ineffective; certainly they are superfluous remedies in the treatment of bacillary dysentery Ipecacuanha, which has been found so servicable in India, Africa, Brazil, and elsewhere, and is recommended even now by many writers, has a very poor place as a dysenteric remedy. Ipecacuanha sine emetina is, generally speaking, unsatisfactory too. The astringents are also unsuitable in the stage of inflammation.

Treatment of Chronic Dysentery.—The chronic form is to be considered rather as a subsequent disease, because in this stage the dysentery bacillus has disappeared for some time from the stools and only mucus or pus is passed. This form of dysentery is very obstinate and recovery is difficult. We can try several remedies by enemata, as silver nitrate (in dilution of 1 to 500 to 1,000), tannin (.25 to .5 per cent. solution), thymol (1 to 500 to 1,000 dilution), resorcin (1 to 2 per cent.), creolin (1 to 2 per cent.), lysol (1 per cent.), and the like. In some cases the author has tried enemata with gum Arabic mixed with bismuth, gallate of bismuth, or iodo-

[1] Plehn: *Deutsch med. Woch.* 1901, No. 39.

form with better results (mucilage of acacia and water āā 50 cc., bismuth subnitrate or gallate 5 gm., or iodoform 0.5 gm.). As an internal remedy we often order salol, tannigen, etc.

Serum Treatment.—*Immunization of Horses against the Dysentery Bacillus.*—An agar culture of the dysentery bacillus which has been maintained at incubator temperature for twenty-four hours is emulsified in normal saline solution and heated at 60° C. for half an hour. Gay prefers instead of heat, the use of a 0.5 per cent. mixture of tricresol with glycerine. The mixture is then inoculated subcutaneously into horses in the usual manner, beginning with small doses, which are gradually increased in amount. For immunization the bacillus must be virulent, and the same rule seems to exist as is reported by some writers in the immunization for streptococcus; namely, that the bacillus isolated directly from the patient is more virulent and effective in the preparation of serum than the bacillus obtained after passage through animals. The author therefore always preserves the direct stick agar culture of the first generation isolated from the stools for immunization. The bacillus kept thus in the ice chest lives for two or three months.

Animal Determination of Dysentery Serum.—For the estimation of the effective power of dysentery serum, mice are well fitted and convenient to use. Five times the lethal dose of a dysentery bacillus culture (0.4 mgr. $=\frac{1}{5}$ normal loop) is mixed with several doses of the serum and injected into the peritoneal cavity of the animal. Our dysentery serum contains more than 40 I E.[1] Todd and Rosenthal produced an antitoxic serum of a very high value, having immunized the horse with the toxin of a bouillon culture of the dysentery bacillus. It is very interesting that the serum of the horse immunized by young bacilli has a high antitoxic power also; this serum protects the animal both against lethal doses of the toxin, and against the infection of the bacillus as well.

Practical Serum Treatment.—The dysentery serum is bactericidal as well as antitoxic (Todd, Rosenthal, Kraus). The treatment with this serum, therefore, has much more effect on dysentery than a serum in the case of typhoid fever. Moreover, the localization of the disease gives much more prospect for treatment. In dysentery the lesions are usually localized in the rectum and lower portion of the large intestine, the physiological function of which is principally mechanical, and where the absorption of food does not take place as in the small intestine. The toxic symptoms are intimately connected with this localization, against which bactericidal serum is valueless. Such symptoms in dysentery are happily less prominent than in typhoid fever. This conception also accounts for the very unfavorable prognosis in entero-dysentery. It is already reported that there is a fitted complement in the human body for the dysentery serum.[2] This is advantageous for the use of a dysentery serum of bactericidal nature. The dysentery serum is therefore the first need in the treatment as a bactericidal agent, which satisfies well the conditions laid down by Ehrlich in the Croonian lecture, 1900.

In accordance with my researches, I have formulated the following rules for the administration of dysenteric serum in the Institute for the Research of Infectious Diseases in Tokio:

[1] That is 0.0025 cc. of serum protects the mice from the infection of five times a lethal dose. If the prophylactic value of the serum is 0.1 cc. for five times the lethal dose of a dysentery culture to mice, then we say that the serum has 1 I E.

[2] Shiga: *Zeitschr. f. Hyg.*, 1902.

1. In mild cases the serum is injected once in a dose of 10 cc.

2. In cases of medium severity the serum is twice injected in doses of 10 cc. The interval is from six to ten hours.

3. In severe cases the largest amounts of serum are injected (about 40 to 60 cc.) but the daily dose does not exceed 20 cc.

By serum treatment the disease in its first stages is quickly cured or markedly ameliorated. In one or two days after the injection, the process is affected, the blood and mucus disappear, pain and tenesmus cease, and the patient seems entirely well. On the later use of the serum (at the end of the first week) improvement of all symptoms occurs on the next day after the injection. The number of stools is markedly diminished, and the tormina and tenesmus decrease. After a few days, remarkable improvement is to be seen. The blood in the stools diminishes or entirely vanishes, the appetite increases, and the general condition is much improved. The recovery happens usually after a week. The effect of the serum upon the fever is very striking; the fever may be lowered even below normal on the next morning after injection in the majority of cases (Shiga, Kruse, Rosenthal). In the ulcerative stage the action of the serum is not so pronounced as in the earlier stages; nevertheless healing of the ulcers with cicatrization often takes place. In such cases, however, the fever is reduced, the number of stools is markedly diminished, the general condition is improved, and the appetite increases. Even in this stage the results obtained are far better than those given by any other method of treatment.

By the serum treatment, the course of the disease is shortened in those who recover, and lengthened in those who otherwise would die. Of the 510 cases treated by the writer (298 with serum and 212 with drugs) the entire course was on the average as follows:

	Recovered	*Died*
Serum treatment	25 days	16 days
Medical treatment	40 days	11 days

The mortality of dysentery under the use of the serum was reduced to one-third, at least less than one-half from that obtained by medical treatment (from 22 to 26 per cent. to 9 to 12 per cent.). Kruse obtained the same results in the few patients treated. In Russia Rosenthal has only had 8 deaths among 157 cases (5.1 per cent. mortality) under serum treatment, while the mortality in Moscow is between 12 and 17.5 per cent. without serum treatment.

Polyvalent Dysenteric Serum.—Practically a polyvalent serum powerful against all types of dysenteric bacilli is highly recommended. The author succeeded in preparing a serum of this kind by alternate immunization of horses with the three types of dysenteric bacilli,—namely the 1st, 2nd and 4th types. Since 1906 he has attained much better results through the use of this serum.

Prophylaxis.—We have already mentioned, in the section on epidemiology, that dysentery bacilli may be carried by flies and the possibility of infection through drinking and also river water. We have also described the existence of the bacillus in the dejecta of convalescents or after recovery. Prophylaxis must be based upon the knowledge of all these points. Here we describe only the protective inoculation.

The author performed active immunization upon himself in 1898. But as a result, it was known to me very soon after that the method is not applicable

generally, because the inoculation of the dead bacilli causes serious inflammation and also general disturbance. After repeated investigation the author came finally to the so-called simultaneous method, in which both the dead bacillus emulsion (heated at 60° C. for thirty minutes) and specific immune serum are simultaneously injected.[1] The animal experiments showed that in fact after one injection of the material, active immunity was procured, guinea-pigs being thus protected against three times the lethal doses for at least three weeks. The simultaneous immunization upon human individuals is also accompanied with only a slight reaction, and is performed as follows: taking the whole quantity of the bacilli from an agar slant culture after twenty-four hours, mixed with 10 cc. sterile normal saline solution and heated at 60° C. for half an hour, we mix it with the same quantity (10 cc.) of immune serum. The mixture thus obtained is used for the first injection. Five days later the second mixture, containing the bacillus emulsion and serum in the ratio of 4 to 1, is injected. The doses for certain ages are as follows:

6 to 15 years	0.4 to 0.8 cc.
16 to 50 years.....	0.8 to 1.0 cc.
50 years and over	0.6 to 0.8 cc.

In the blood serum of individuals thus treated the presence of the protective body was proved after twenty days, and even after thirty days in the animal experiment. In the years 1898–1900 the author tried preventive inoculation in this manner on about 10,000 men in the district of Japan where epidemic dysentery prevails most seriously, and was able to diminish the mortality in the district from 20 to 30 per cent. to about zero.

By protective inoculation the mortality has decreased but not been entirely abolished. Considering the fact that local immunity has a better result in the protection of the intestinal infectious diseases, the author made experiments in applying the heated emulsion to rabbits per os to protect them from the disease. These experiments showed that this direct immunity of the mucous membrane of the bowels is the best for the purpose. Thus we have reason to prefer this to inoculation, because the author's method does not cause any illness and at the same time is a more convenient way of application.

The only disadvantage of preventive inoculation is that we can obtain the immunity only after an interval of eight days after inoculation, while the duration of the immunity is only about two months. Therefore the author recommends the injection of immune serum in small quantity (5 to 8 cc.), if we require to get the protective power quickly in case of family epidemics.

[1]Shiga: "Ueber Versuche zur Schutzimpfung gegen die Ruhr.," *Deutsch. med. Woch.*, 1903, No. 18.

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